CHEMICAL REVIEWS

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Review

Catalytic Enantioselective Functionalizations of C−H Bonds by Chiral Iridium Complexes

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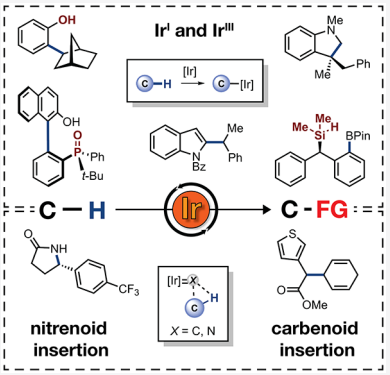
ABSTRACT: The development of catalytic enantioselective transformations, enabling the construction of complex molecular scaffolds from simple precursors, has been a long-standing challenge in organic synthesis. Recent achievements in transition-metal catalyzed enantioselective functionalizations of carbon−hydrogen (C−H) bonds represent a promising pathway toward this goal. Over the last two decades, iridium catalysis has evolved as a valuable tool enabling the stereocontrolled synthesis of chiral molecules via C−H activation. The development of iridium-based systems with various chiral ligand classes, as well as studies of their reaction mechanisms, has resulted in dynamic progress in this area. This review aims to present a comprehensive picture of the enantioselective functionalizations of C−H bonds by chiral iridium complexes with emphasis on the mechanisms of the C−H activation step.



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1. INTRODUCTION

Carrying out selective chemical transformations on readily accessible, yet very unreactive, materials such as hydrocarbons has been a long-standing objective of organic synthesis, which has intrigued chemists for several decades.[1] This has led to the development of new technologies enabling activation and functionalization of carbon−hydrogen (C−H) bonds, which are ubiquitous in organic molecules. The constant progress in this field continuously alters chemists' approaches to building molecules, often offering elegant, atom- and step-economic alternatives to strategies which rely on the manipulations of functional groups,[2] as well as providing new synthetic opportunities. Specific C−H bonds are often viewed as latent equivalents of various functional groups, which can be activated by an appropriate reagent or a catalyst. This provides a growing number of new and unconventional disconnections, constantly reshaping our perspectives in retrosynthetic analysis.[3−7] The selective functionalization of enantiotopic C−H bonds is a particularly valuable strategy, allowing for the construction of chiral molecules with a well-defined three-dimensional spatial arrangement.[8−12] These structures are widely sought after due

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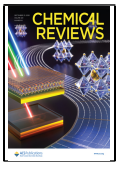

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to their biological significance, and they find widespread application in the pharmaceutical[13] and agrochemical[14] industries.

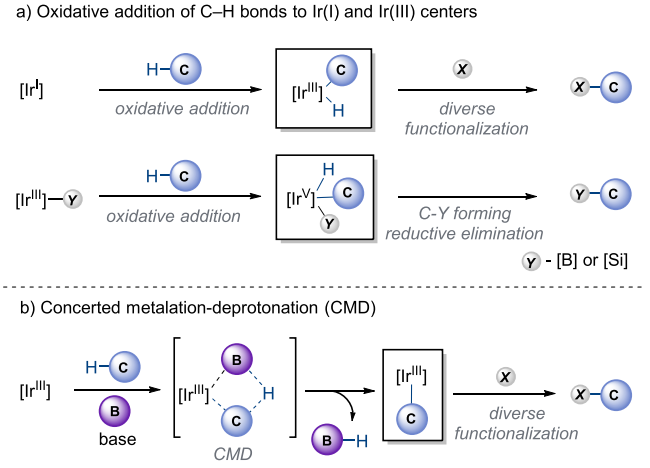
Transition-metal complexes dominate the field of C−H functionalization, as they enable the modification of a wide array of inert C−H bonds.[15] Among different metals, iridium complexes have played a particularly important role in the evolution of C−H functionalization methodologies, especially for the understanding of the fundamental organometallic mechanisms behind these processes.[16] Iridium offers various modes of substrate activation, which are also common for rhodium and cobalt, which are located above iridium in the periodic table. The reactivities of the group 9 metal catalysts, however, often diverge. Their reaction pathways are influenced by different electronegativities, ionization potentials, or strengths of the metal−ligand bonds. Iridium tends to form stronger metal−carbon and metal−hydrogen bonds than the corresponding rhodium and cobalt analogs.[17] This correlates with the thermochemistry of the C−H insertion processes, which influences the selectivities with which the group 9 metal complexes react with different types of C−H bonds.[18] The strong binding of iridium to the transformed hydrocarbons can be viewed as a mixed blessing. The formation of stable iridium complexes allowed for the early characterization of key intermediates in the C−H functionalization processes.[19,20] Conversely, the high stabilities of many organoiridium species may hamper their further transformation and thus potentially limit their utility in catalysis. In spite of this, there are many iridium catalyzed C−H functionalization processes with good to high turnover numbers. To fully harness their potential, however, it is essential to achieve a precise structural control of the functionalization of enantiotopic C−H bonds and apply this technology for the stereoselective synthesis of chiral molecules.

Herein we summarize developments of enantioselective C−H functionalization methodologies catalyzed by iridium complexes. Enantioselective transformations comprised of more than one catalyst where the iridium complex does not transfer the chiral information to the product, are not discussed in this review.[21] Allylic substitution reactions involving electron-rich arenes, which represent a formal activation of C−H bonds, are also not examined here and are covered elsewhere.[22] We structured the following discussion based on the substrate activation modes, which differ in the mechanism of the C−H activation step. This review presents transformations reported up until May 2020.

2. INNER-SPHERE C−H FUNCTIONALIZATION

Transformations involving the direct interaction of a transition metal with a C−H bond, leading to the formation of a discrete organometallic intermediate, are referred to as inner-sphere[23] or organometallic[24] C−H functionalization approaches. Subsequent functionalization of the resulting transition-metal alkyl or aryl species yields the product (Scheme 1a). Several pathways of inner-sphere C−H bond activation have been distinguished.[25,26] While iridium(I) complexes typically undergo a facile C−H oxidative addition (Scheme 1a), the iridium(III) species can activate C−H bonds via both oxidative and nonoxidative mechanisms. The oxidative addition of C−H bonds, which leads to a congested iridium(V) species,[27] has been proposed for C−H silylation[28] and borylation[29] processes (Scheme 1a). The nonoxidative C−H activation involves cooperative action of the iridium(III) complex and a base cocatalyst in a concerted

Scheme 1. Mechanistic Classification of Iridium-Catalyzed Inner-Sphere Enantioselective C−H Functionalization Reactions: (a) C−H Activation Involving Oxidation of the Iridium; (b) C−H Activation without Changing the Iridium Oxidation State



metalation-deprotonation (CMD) process (Scheme 1b).[30] The following section describes transformations, which are believed to proceed via C−H activation at iridium(I) and iridium(III) centers.

2.1. C−H Oxidative Addition to Iridium(I) Complexes

2.1.1. Functionalization of C(sp^2)−H Bonds. The first iridium catalyzed enantioselective functionalizations of C−H bonds were documented at the beginning of this century. Togni and co-workers demonstrated that the iridium(I) system, originally developed for the enantioselective hydroamination of norbornenes via activation of N−H bonds,[31] is also suitable for the enantioselective functionalization of C−H bonds (Scheme 2). In this reaction, an iridium complex bearing cyclopentadienyl (Cp) and a chiral 2,20-bis(diphenylphosphino)-1,10-biphenyl derived ligand (*R*)-MeO-BIPHEP catalyzes an intermolecular hydroarylation of norbornene **2** with benzamides to give product **3** with a high enantiomeric excess (94% ee), however in a very low yield (12%).[32] Activation of the benzamide substrate by the 18-electron [Ir(Cp)(*R*)-MeO-BIPHEP] complex requires dissociation of one of the ligands, which likely takes place by the Cp ring changing its hapticity from η^5 to η^3. In 2003, Dorta, Togni, and co-workers reported an iridium catalyzed addition of phenols across the norbornene to give **4**, however, with very low enantiomeric excess (4.5% ee).[33] Five years later Shibata and co-workers disclosed an example (product **5**) of an enantioselective C−H functionalization of 2′-methylacetophenone with norbornene in the presence of a cationic iridium complex formed from $[Ir(cod)_2]BF_4$ and ((*R*)-MeO-BIPHEP).[34]

Two related, albeit fundamentally different, mechanisms of the iridium-catalyzed hydrofunctionalization of olefins have been proposed (Scheme 2). Both pathways start with the oxidative addition of the C−H bond to the iridium(I) complex leading to iridium(III) hydride **6**. The following steps differentiate the two scenarios. The olefin insertion into the Ir−H bond followed by the C−C bond-forming reductive elimination is referred to as a Chalk−Harrod mechanism.[35] The second scenario involves migratory insertion into the Ir−C bond, leading to iridium hydride **10**, which undergoes a subsequent C−H bond-forming reductive elimination to form

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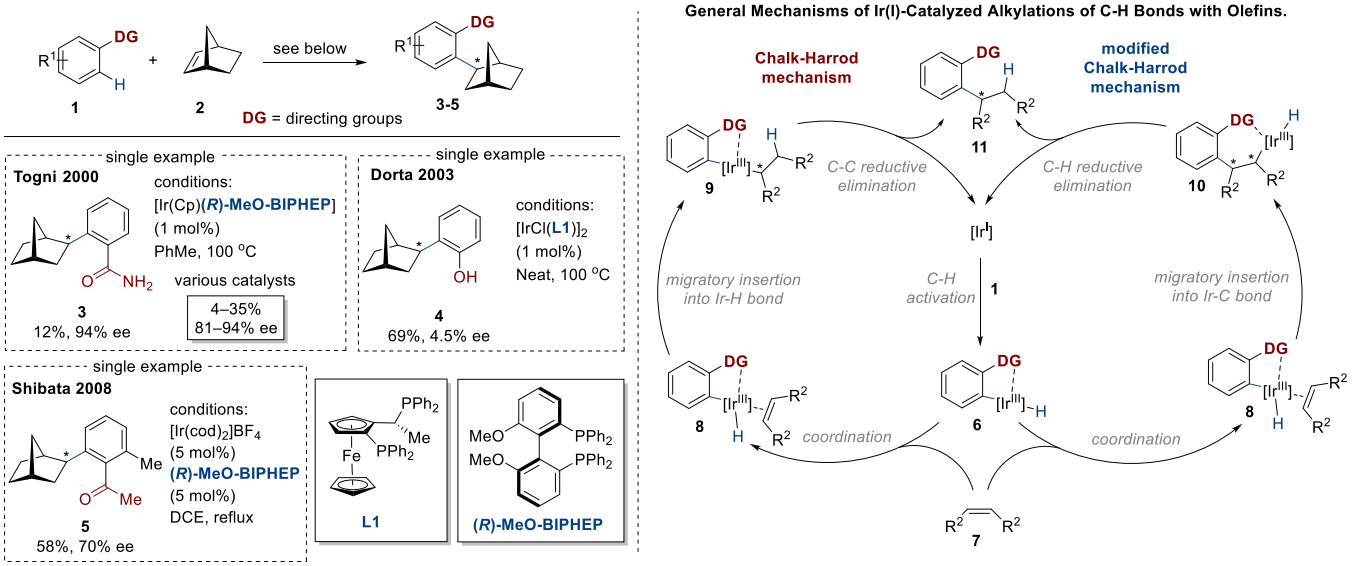
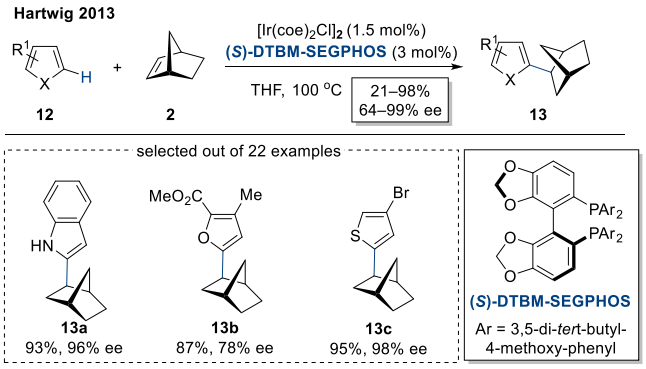
Scheme 2. Early Examples of the Enantioselective Hydroarylation of Norbornene and General Mechanisms of the Ir(I)-Catalyzed Hydroarylations of Olefins via C−H Activation



product **11** (modified Chalk−Harrod mechanism). Several mechanistic studies suggest that the modified Chalk−Harrod mechanism is favored in iridium systems[36−38] and that C−C bond-forming reductive eliminations from iridium(III) centers are very challenging.[39]

In 2013, Hartwig demonstrated a highly enantioselective addition of the C−H bonds of heteroarenes to norbornene and norbornadiene (Scheme 3).[40] The reaction occurs selectively on

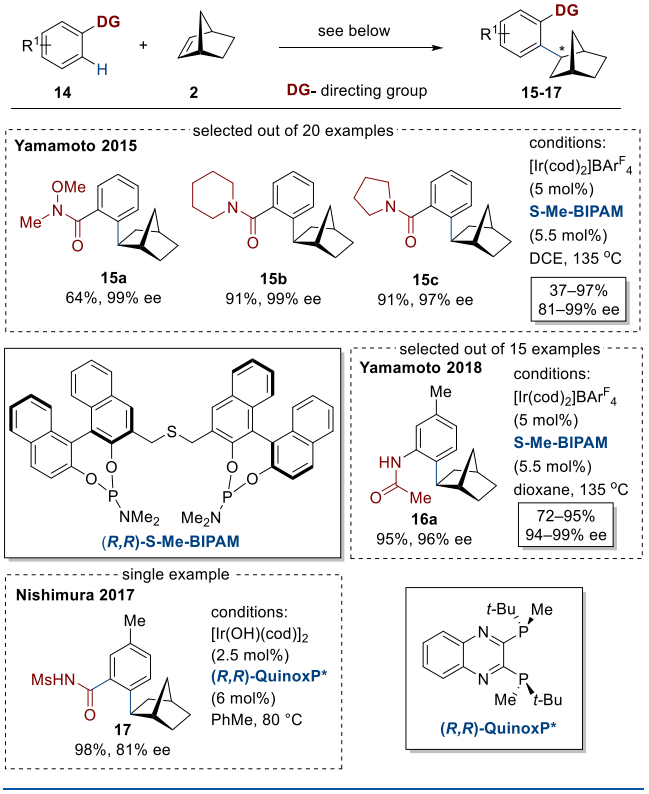
Scheme 3. Enantioselective Hydroheteroarylation of Bicycloalkenes



the C−H bonds adjacent to the heteroatoms, even in the case of unprotected indoles **12**, which typically react at the C3 position. A catalytic amount of iridium(I) complex $[Ir(coe)_2Cl]_2$ and (*S*)-DTBM-SEGPHOS (DTBM- 3,5-di-*tert*-butyl-4-methoxy) ligand converts various indoles, thiophenes, pyrroles, and furans into the alkylated products **13** with low to excellent yields (21−98%) and moderate to excellent enantioselectivities (64−99% ee). Mechanistic studies indicated that the oxidative addition of the heteroarene C−H bond is fast and takes place before the rate-determining step. The modified Chalk−Harrod mechanism has been proposed for this transformation.

Yamamoto and co-workers applied their iridium/Me-BIPAM (bis(phosphoramidite)) catalytic system[41] to achieve a highly enantioselective hydroarylation of norbornene **2** through an amide and ketone directed C−H activation (Scheme 4).[42] The

Scheme 4. Highly Enantioselective Hydroarylations of Norbornenes



new sulfur-linked bis(phosphoramidite) ligand (*R,R*)-S-Me-BIPAM enabled C−H alkylation of various aromatic amides and ketones into products **15** with low to excellent yields (37−97%) and high enantioselectivities (81−99% ee). Deuterium labeling studies, including a kinetic isotope effect (KIE) of 2.08, indicated that the C−H activation is the irreversible, turnover-limiting step of this reaction. The same group further extended their catalytic system to the asymmetric alkylation of aniline derivatives.[43] The iridium catalyst, bearing the (*R,R*)-S-Me-BIPAM ligand, converted variously substituted acetanilides to

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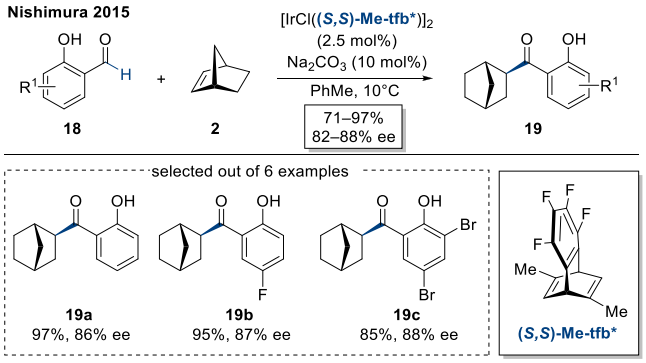
the norbornene derived products **16**, with high yields (75−95%) and enantioselectivities (94−99% ee). In 2017, Nishimura and co-workers reported an iridium catalyzed C−H alkenylation and alkylation of *N*-sulfonylbenzamides.[44] The authors demonstrated that the chiral phosphine (*R*,*R*)-QuinoxP* is a promising ligand for controlling the enantioselectivity of the alkylation process, showcased in the formation of **17** as the sole example.

In 2015, Nishimura reported the enantioselective alkylation of the aldehydic C−H bonds of 2-hydroxybenzaldehydes **18**, catalyzed by the iridium complex bearing chiral diene ligand (*S*,*S*)-Me-tfb* (Scheme 5).[45] This strategy allows for the direct

Scheme 5. Enantioselective Hydroacylation of Norbornene with 2-Hydroxybenzaldehydes

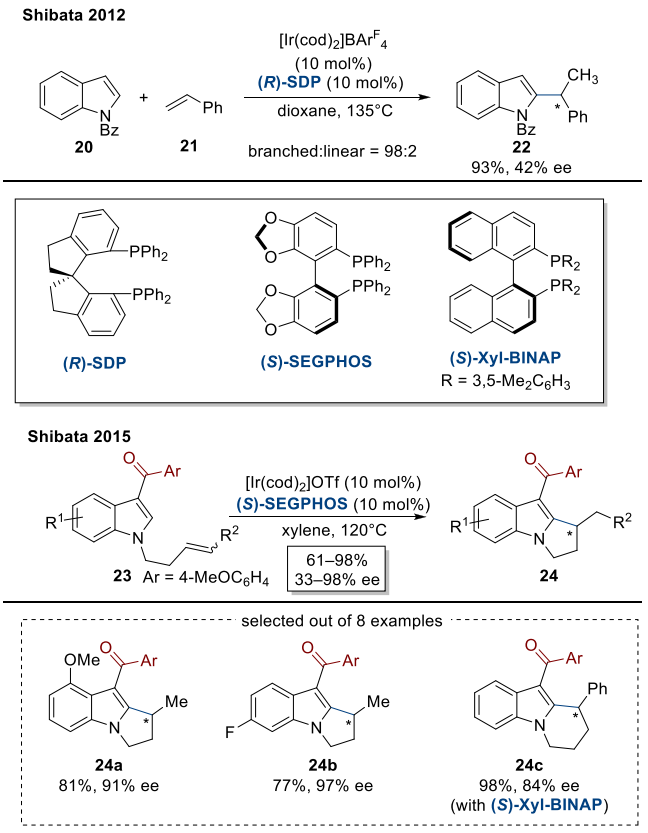


alkylation of 2-hydroxybenzaldehydes in high yields (71−97%) and relatively good enantioselectivities (82−88% ee). The authors demonstrated that the hydroxyl group at the C2 position is essential for reactivity, due to the envisioned phenoxoiridium(I) intermediate that assists in the activation of the acyl C−H bond.

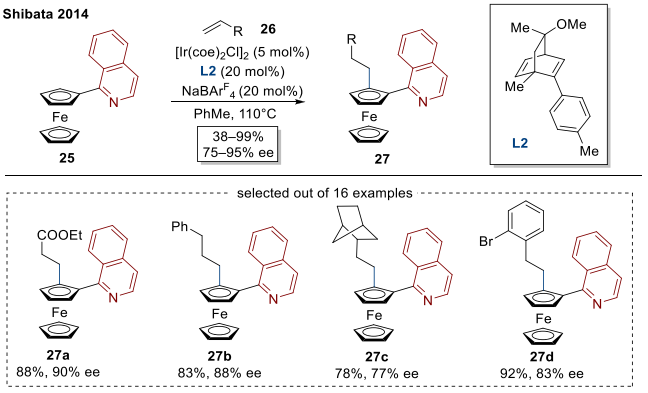
Iridium catalyzed enantioselective alkylations of C−H bonds have further been developed by employing various olefin coupling partners, beyond the scope of the norbornene derivatives. In 2012, Shibata and co-workers developed an intermolecular C2-alkylation of *N*-protected indoles with terminal alkenes **21** to give linear or branched alkyl indoles.[46] Only one asymmetric example, **22**, was provided, with moderate enantioselectivity (42% ee), using benzoyl-protected indole **20** and the bisphosphine (*R*)-SDP as the chiral ligand (Scheme 6). Subsequently, a highly enantioselective intramolecular version of this process was realized by the same group in 2015 (Scheme 6).[47] In this reaction a *para*-anisoyl group, located at the C3 position of indole **23**, directs the iridium catalyst in the C−H activation step. The combination of a cationic iridium(I) species and (*S*)-SEGPHOS or (*S*)-Xyl-BINAP as ligand enabled this process with high yields (61−98%) and enantioselectivities (33−98% ee).

The Shibata group developed the C−H alkylation methodology to induce planar chirality in ferrocenes.[48] The combination of a chiral diene ligand **L2** and isoquinoline as effective directing groups allowed for the highly regio- and enantioselective C−H alkylation of ferrocene derivatives **25** (Scheme 7). This was the first example of an iridium-catalyzed enantioselective C(sp^2)−H alkylation to furnish enantioenriched ferrocenes. Notably, various functionalities on the olefin partners such as esters and aryl and alkyl groups were well tolerated, rendering products **27** with moderate to excellent yields (38−99%) and high enantioselectivities (75−95% ee).

Scheme 6. Enantioselective C−H Alkylation of Indole Derivatives



Scheme 7. Enantioselective C−H Alkylation of (Isoquinolin-1-yl)ferrocenes



In 2017, Shibata reported an enantioselective C−H alkylation of acetanilides with β-substituted acrylates **29**. This formal C−H conjugate addition allowed for the synthesis of chiral δ-amino-acid derivatives **30** in yields ranging from 11% to 99% and good to excellent enantioselectivities (73−99% ee) (Scheme 8).[49] Two chiral bisphosphine ligands were utilized in the development of the scope. The (*S*,*S*)-Chiraphos generally gave higher yields than the (*S*)-Difluorphos ligand, while the latter afforded superior enantioselectivities (>95% ee). In 2018, the same group extended this methodology to an intramolecular variant employing an ester tether.[50] In this case, benzoyl amide outperformed the acetamide in terms of enantiocontrol. The classical chiral (*S*)-BINAP ligand was applied to furnish enantioenriched γ-lactones **33** bearing all-carbon quaternary

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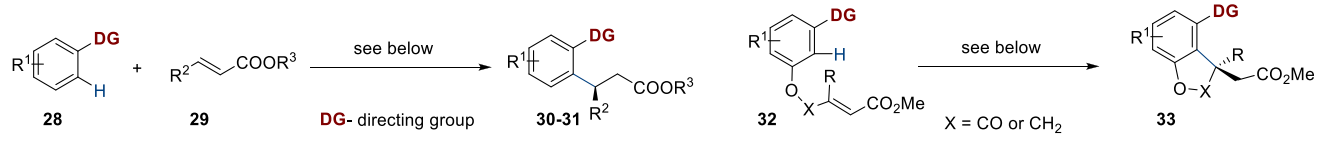
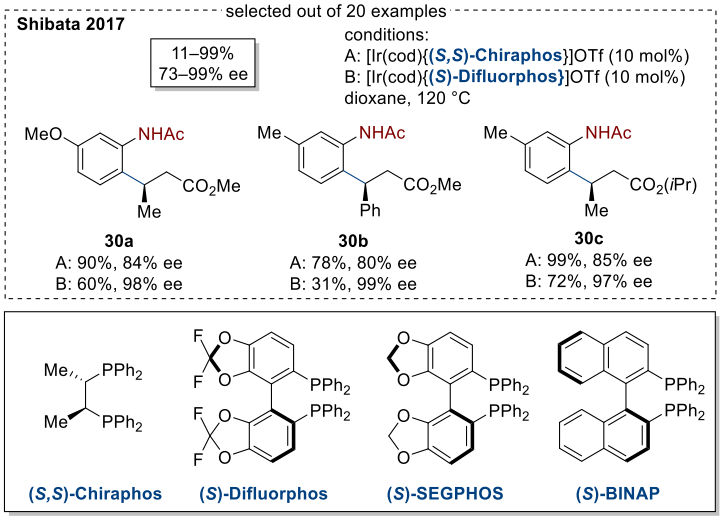
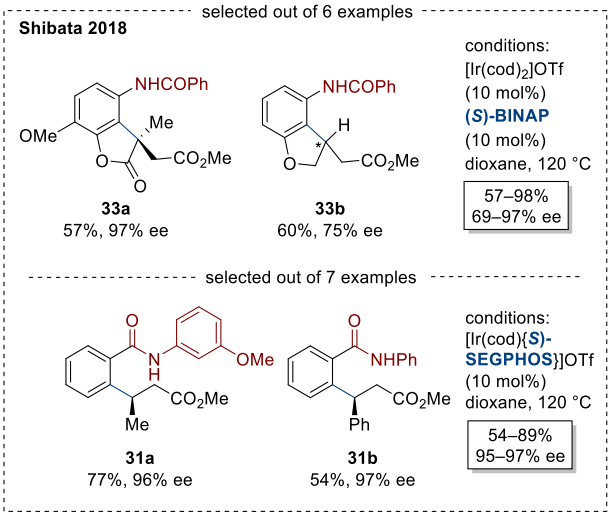
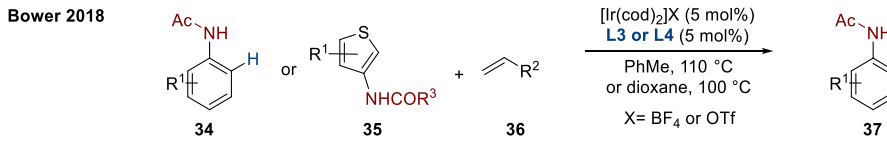
Scheme 8. Enantioselective Addition of Anilide and Amide *ortho*-C−H Bonds across Acrylates

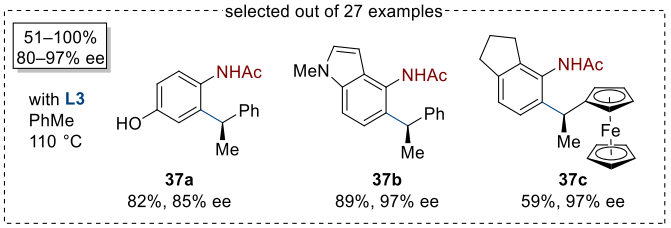


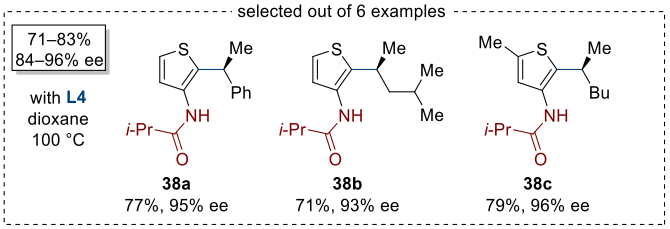


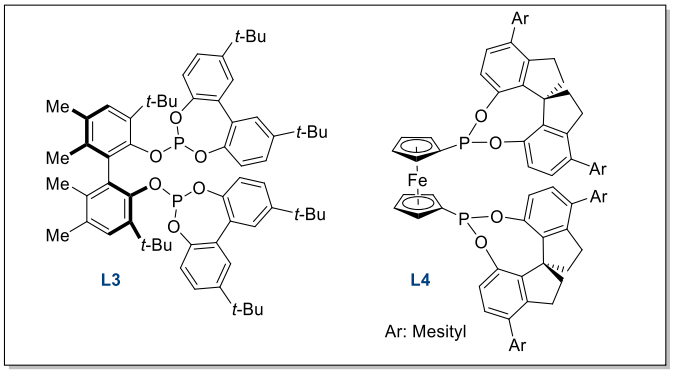


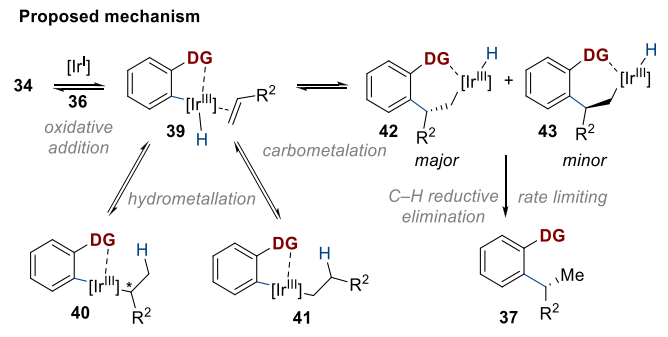
Scheme 9. Enantioselective Hydroarylation of Styrenes and α-Olefins via C−H Activation of Anilides











stereogenic centers with moderate to excellent yields (57−98%) and enantioselectivities (69−97% ee) as well as dihydrobenzofuran **33b** (60%, 75% ee). The authors also utilized the *N*-aryl carbamoyl directing group for the development of an intermolecular reaction. In this case, the (*S*)-SEGPHOS ligand enabled the formation of the *ortho*-alkylated products **31** with good yields (54−89%) and excellent enantioselectivities (95−97% ee). Deuterium incorporation studies of the intermolecular reaction indicated that the C−H bond cleavage and alkene insertion proceed at the *ortho* positions of both of the substrates' phenyl rings, but the subsequent reductive elimination step occurs only at the arene bearing the carbonyl group. As a result, the regioselective *ortho* C−H alkylation to furnish products **31** was observed.

Bower and co-workers disclosed a highly branch-selective and enantioselective hydroarylation of a wide range of styrenes and α-olefins **36** via the C−H activation of anilide derivatives (Scheme 9).[51] The authors developed a class of chiral

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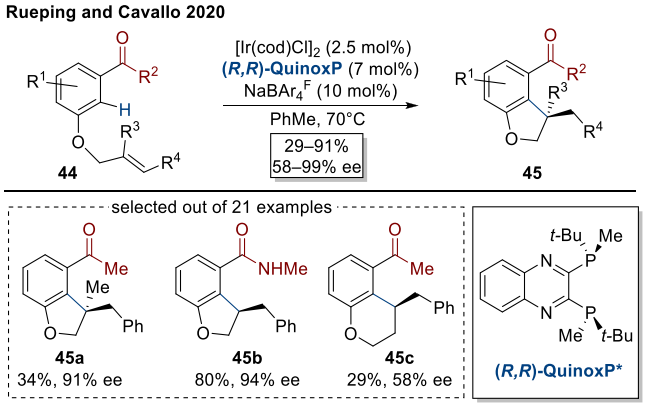
biphosphite ligands **L3**, which enables the C−H alkylation with moderate to excellent yields (46−100%) and high enantiomeric excesses (80−97% ee). The broad scope of products **37** includes the functionalization of indole-based or halogen-substituted substrates, as well as steroid-derived olefins. Tailoring of the ligand structure led to **L4**, which allowed application of this catalytic system to access thiophene derivatives **38** without compromising the yields and selectivities. Mechanistic studies, including natural abundance ^{13}C KIE,[52] support the modified Chalk−Harrod mechanism and indicate that the C−H reductive elimination is an irreversible rate-determining step, while the carbo- and hydrometalations are reversible.

Recently, Rueping, Cavallo, and co-workers described an intramolecular hydroarylation of internal olefins using a cationic iridium(I)/(*R*,*R*)-QunioxP* catalyst system.[53] This protocol enables the rapid access to the biologically important chiral dihydrobenzofurans **45** (Scheme 10) through an amide and

Scheme 10. Enantioselective Intramolecular C−H Alkylation Using Ketone and Amide Directing Groups

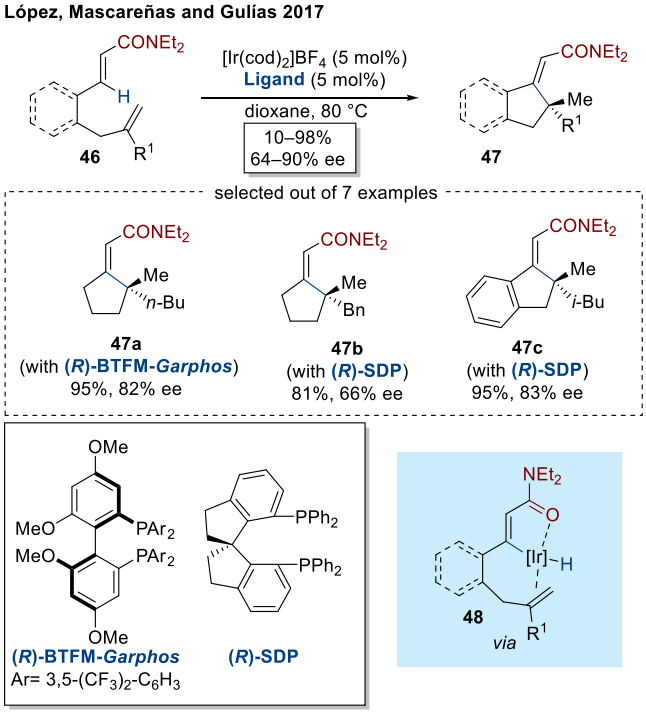


ketone directed C−H activation. Products containing tertiary benzylic stereocenters were obtained with low to good yields (29−91%) and moderate to excellent enantioselectivities (58−99% ee). The authors demonstrated that this method allowed for the formation of a quaternary stereocenter in product **45a**, with high enantiomeric excess (91% ee), albeit with low yield (34%).

In 2017, López, Mascareñas, and Gulías reported an iridium-based catalytic system for the enantioselective functionalization of C−H bonds of various alkenes (Scheme 11).[54] The authors developed an amide-directed intramolecular hydrocarbonation of alkenes **46** to access cyclopentanes and indanes bearing quaternary stereocenters. The commercially available bisphosphine ligands (*R*)-BTFM-Garphos or (*R*)-SDP delivered products **47** with yields ranging from 10% to 98% and good enantioselectivities (64−90% ee).

In 2013, Hayashi and Nishimura disclosed a unique enantioselective [3 + 2] annulation via C−H activation between *N*-acyl ketimines and 1,3-dienes **50**, employing an iridium(I) catalyst bearing chiral (*S*,*S*)-Me-tfb* diene ligand (Scheme 12).[55] The postulated catalytic cycle commences with the formation of ketimine **52** from the 3-aryl 3-hydroxyisoindolin-1-one substrate **49**. Next, the nitrogen-directed C−H oxidative addition, followed by deprotonation by DABCO, leads to complex **54**. Due to the steric repulsion of one of the methyl groups on the (*S*,*S*)-Me-tfb* ligand, the diene **50a** approaches the iridium center from the *Re*-face of the imine (back side), and

Scheme 11. Enantioselective Intramolecular Functionalization of Alkene C−H Bonds



the less substituted alkene coordinates to the iridium center to deliver intermediate **55**. Subsequently, oxidative cyclization of a more substituted alkene moiety of the diene with the imine forms a π-allyl iridium(III) intermediate **56**, which undergoes a reductive elimination and protonolysis to furnish product **51** and regenerates the cationic iridium complex **53**.

In 2016, Nishimura expanded the enantioselective [3 + 2] annulation employing internal alkynes **58** as the acceptors and (*R*)-BINAP as ligand (Scheme 13).[56] Spiroaminoindene derivatives **59** were afforded with yields ranging from 8% to 98% and with enantioselectivities from 1% ee to 93% ee. The authors discovered that the addition of a catalytic amount of benzoic acid significantly alters the stereochemical outcome of the reaction. The exact role of this additive, however, remains unclear. In 2018, the same group disclosed the use of 1,3-enynes **60** to access the corresponding alkyne-substituted aminoindanes **61**.[57] Using an iridium catalyst bearing the chiral diene (*S*,*S*)-Me-tfb* afforded the products as single regio- and diastereoisomers **61** with moderate to high yields (39−96%) and excellent enantioselectivities (>98% ee). The proposed catalytic cycle closely follows the mechanism previously postulated by Hayashi and Nishimura (Scheme 12).

In addition to C−H alkylations with neutral or electron-poor olefin partners, iridium catalysis is a valuable tool for C−H additions across electron-rich carbon−carbon double bonds (C=C). In 2015, Nishimura and co-workers disclosed an iridium catalyzed hydroarylation of vinyl ethers **63** via directed activation of aromatic C−H bonds (Scheme 14).[58] The reaction affords selectively branched products, bearing ether-containing stereocenters. Initial studies toward the development of an enantioselective variant of this process indicated chiral diene (*S*,*S*)-Fc-tfb* as a promising ligand for this task, giving the desired chiral ether **64** with good yield (80% yield) and moderate enantiomeric excess (77% ee). One year later, the same group developed a highly enantioselective alkylation of *N*-

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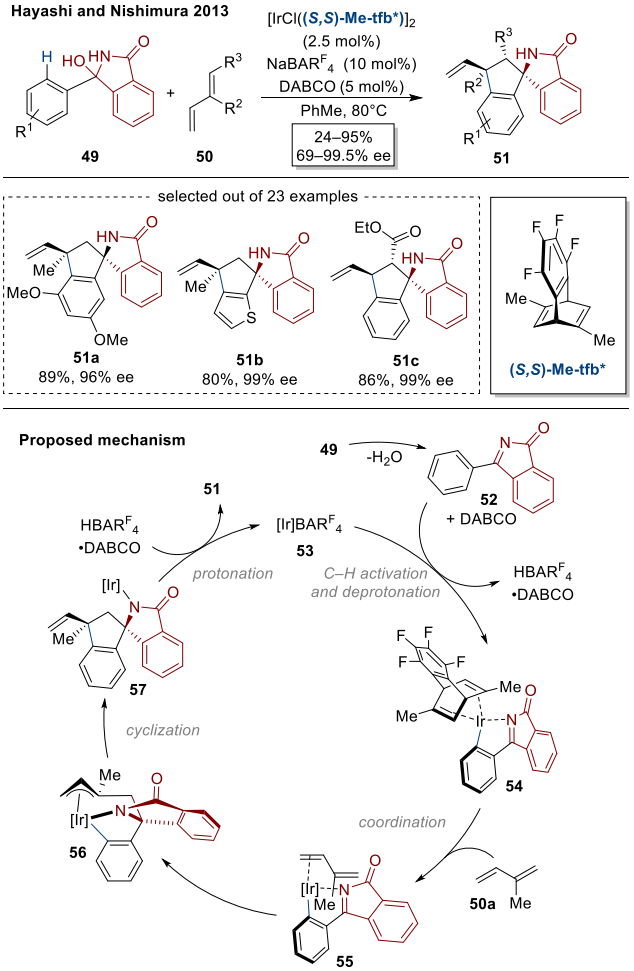
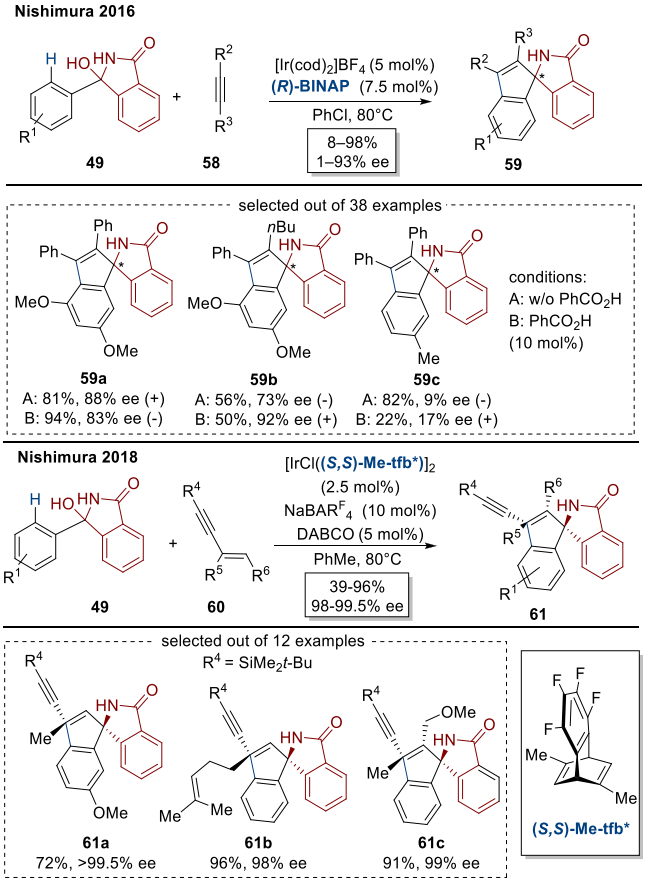
Scheme 12. Enantioselective [3 + 2] Annulation via C−H Activation between *in situ* Generated Ketimines and 1,3-Dienes



Scheme 13. Enantioselective [3 + 2] Annulation via C−H Activation between *in Situ* Generated Ketimines and Alkynes or 1,3-Enynes



sulfonylbenzamides with vinyl ethers.[59] In this reaction, an iridium complex possessing chiral diene (*S,S*)-Me-tfb* catalyzes the formation of the hydroarylation products **65** with good yields (9−97% yield) and high enantioselectivities (82−99% ee). Deuterium experiments indicated that the C−H activation and hydrometalation steps (from **67** to **68**) are reversible. Computational studies performed by Huang provided more insight into the mechanism of the hydroarylation, indicating that the irreversible carbometalation leading to **69** is the rate- and selectivity-determining step.[37] The subsequent C−H bond-forming reductive elimination yields products **64**−**66**. Nishimura and co-workers further extended this methodology to the functionalization of aryl-substituted azoles containing N−H bonds such as pyrroles, imidazoles, indoles, and benzimidazoles.[60] Chiral diphosphine ligands were found to be effective for this substrate class. A catalytic amount of iridium(I) complex and the (*R,R*)-QuinoxP* ligand enabled access to hydroarylated products **66** in good yields (54−99%) and enantiomeric excesses (3−98% ee).

Recently, Lassaletta, Ros, López-Serrano, Fernández, and coworkers reported a highly regio-, diastereo-, and enantioselective hydroarylation of vinyl ethers and bicycloalkenes through C−H functionalization of heterobiaryls **70** (Scheme 15).[61] The reaction takes place with simultaneous installation of central and axial chirality, with good to excellent stereocontrol, forming exclusively the branched products **72**. This method allows for the hydroarylations of a wide array of vinyl ethers **71** with high yields (33−95%) and stereoselectivities (10:1−>20:1 dr, 53−99% ee). Functionalization of 2,3-dihydrofuran delivers products (*e.g.* **72c**) with moderate yields (35−76%) and low diasterocontrol (2:1−3.5:1 dr), however with very high enantiomeric excesses for the major diastereoisomers (92−98% ee). This catalytic system was also applied for the hydroarylation of norbornenes to selectively access *exo*-products **73** with high yields (44−99%) and enantioselectivities (80−99% ee). The authors performed detailed mechanistic studies, which support the modified Chalk−Harrod mechanism and provide insights into the stereoselectivity of the process.

Nishimura and co-workers further expanded the enantioselective hydroarylation methodology for the synthesis of chiral ethers **77**−**78** (Scheme 16). The new reaction utilizes alkenyl ether substrates **75**, which upon isomerization form the corresponding 1-alkenyl ethers **76**, which undergo the regio- and enantioselective hydroarylation.[62] The reaction takes place in the presence of a catalytic amount of iridium precursor $[IrCl(cod)]_2$, $NaBAr^F_4$ [Ar^F = 3,5-$(CF_3)_2C_6H_3$], and (*R*)-Xyl-BINAP ligand to afford products **77** with high yields (68−99% yield) and enantioselectivities (78−99% ee). Huang and co-workers investigated the detailed reaction mechanism and the origins of the regio- and enantioselectivities of this reaction employing DFT calculations.[38] These studies support the modified Chalk−Harrod-type mechanism, proceeding via the migratory insertion into the Ir−C bond and subsequent C−H

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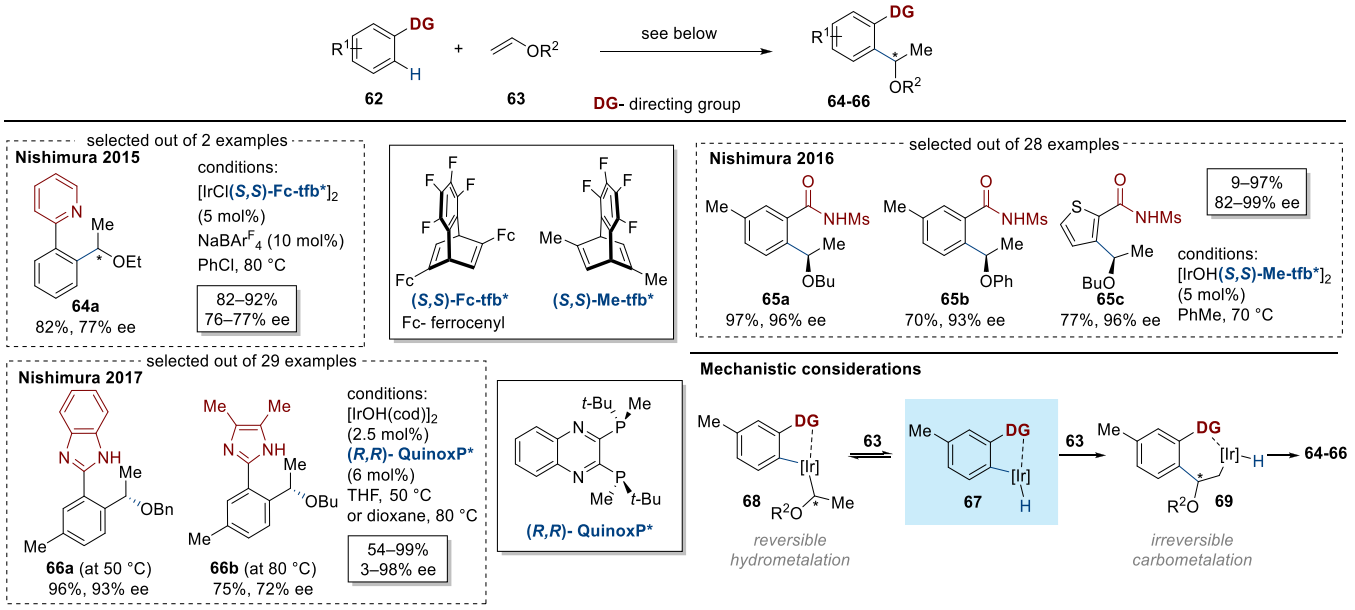
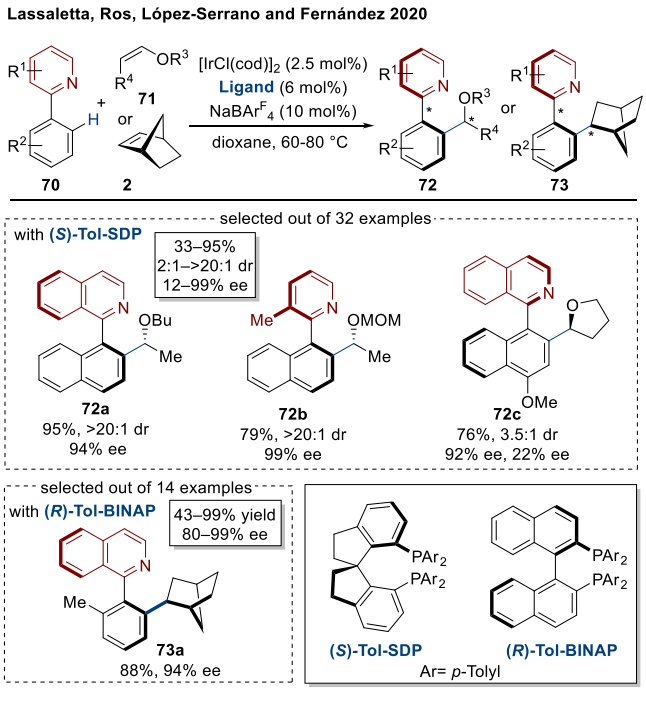
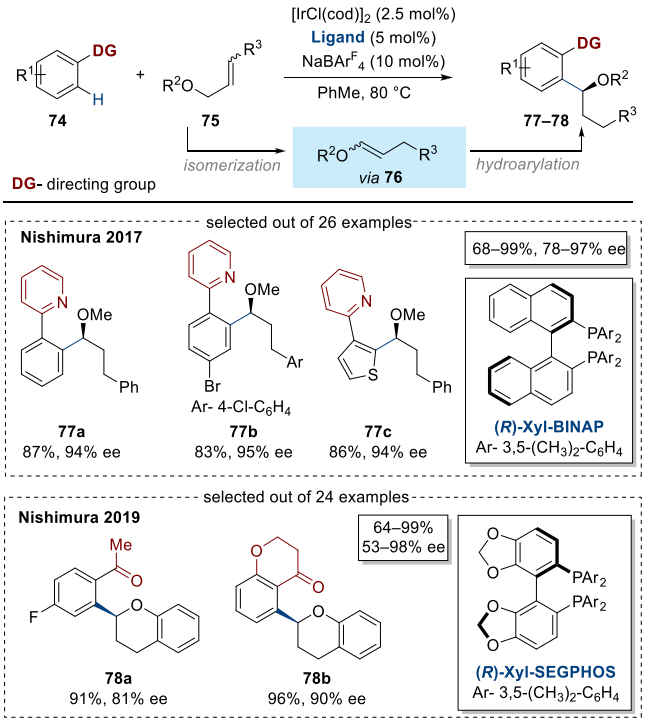
Scheme 14. Enantioselective Hydroarylation of Vinyl Ethers



Scheme 15. Ir-Catalyzed Atroposelective Desymmetrization of Heterobiaryls



Scheme 16. Enantioselective Hydroarylation of Alkenyl Ethers by Olefin Isomerization



reductive elimination, presented in Scheme 2. The hydroarylation strategy through the olefin isomerization has also been applied to access enantioenriched 2-arylchromanes **78**.[63] A cationic iridium complex bearing the (*R*)-Xyl-SEGPHOS ligand enables the asymmetric hydroarylation of 2H-chromenes with aromatic ketones. These two reports represent rare examples of regio- and enantioselective hydroarylations of internal alkenes.

In addition to the processes discussed above, in which the key organoiridium(III) species undergo insertion into C=C bonds, there are a few enantioselective processes involving additions across carbon−heteroatom (C=X) double bonds. The first example was reported by Shibata and co-workers in 2009, employing a chiral bisphosphine (*S*)-H_8-BINAP ligand to obtain the 4-acetyloxindole **80** with a moderate yield (69%) and enantioselectivity (72% ee) (Scheme 17).[64] This transformation was further developed by the Yamamoto group.[41] The use of chiral bidentate bis-phosphoramidite ligand (*R,R*)-Me-BIPAM enabled the formation of products **81** with good to excellent yields (69−99%) and high enantioselectivities (80−98%). Among various carbonyl directing groups evaluated, the amide moiety provided the best performance. The same group performed detailed mechanistic investigations of this process.[65] Based on ^{1}H NMR experiments, kinetic isotope effect (KIE),

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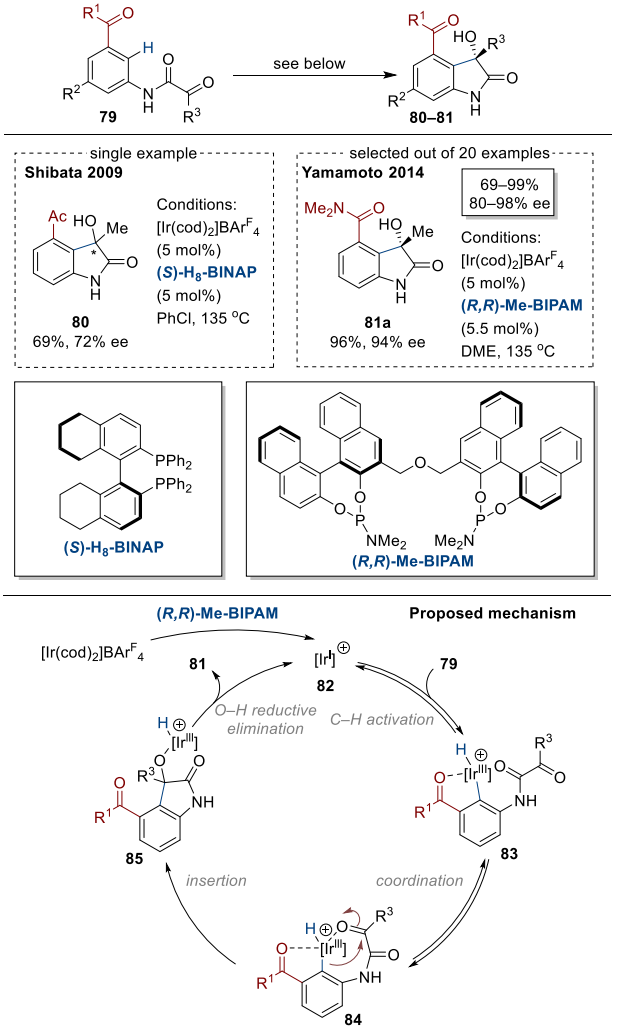
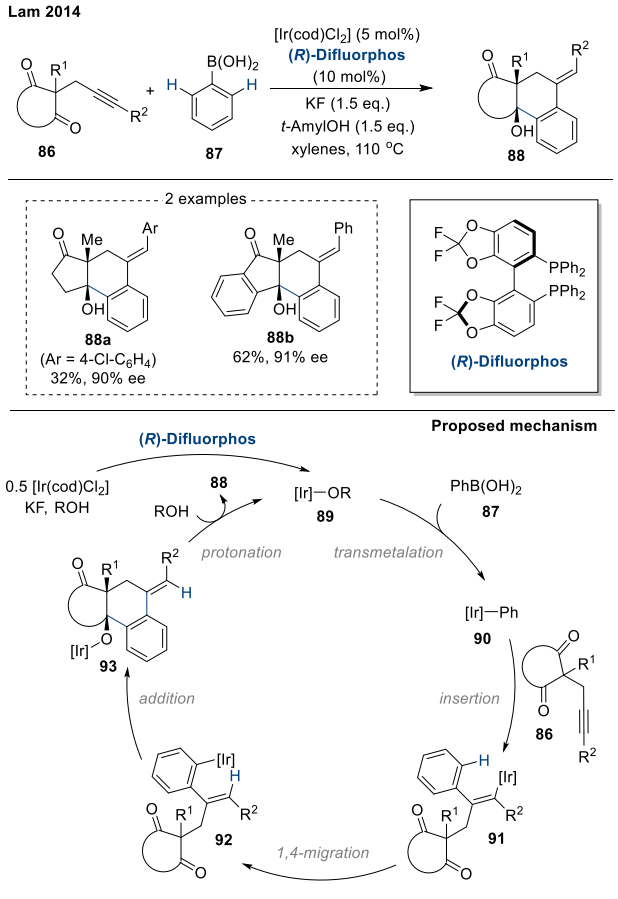
Scheme 17. Ir-Catalyzed Enantioselective C−H Addition to α-Ketoamides



Scheme 18. Enantioselective Arylative Cyclization of Alkynones



and Hammett studies, the authors proposed a catalytic cycle presented in Scheme 17. First, the iridium(I) precatalyst forms a cationic active complex **82** with a chiral bis-phosphoramidite ligand. The deuterium studies, combined with KIE of 1.85, suggest that the following C−H activation is reversible and takes place prior to the rate-determining step. The resulting intermediate **83** is in equilibrium with the complex **84**, from which the rate- and enantio-determining addition to the carbonyl takes place to form the iridium alkoxide **85**. The subsequent O−H bond-forming reductive elimination forms product.

A different iridium catalyzed C−H addition to ketones was disclosed by Lam and co-workers.[66] The authors reported a synthesis of polycycles **88** in the reaction of alkyne-substituted diketones **86** with arylboronic acids (Scheme 18). The proposed reaction mechanism commences with the formation of the iridium-alkoxide species **89**, which undergoes transmetalation with the aryl boronic acid **87**. The resulting aryl iridium complex **90** undergoes insertion into the alkyne, which is followed by a unique 1,4-iridium migration to give the intermediate **92**. The subsequent nucleophilic addition onto one of the ketones generates the iridium alkoxide **93**. Protonation of **93** with alcohol releases the product and regenerates the active iridium complex **89**. The authors demonstrated that the (*R*)-Difluorphos ligand enables this process in a highly enantioselective manner (90−91% ee). The reported yields, however, are moderate (32−62%).

In 2019, Shirai and co-workers reported an example for an asymmetric hydroacylation of 2-acetylbenzaldehyde **94** to give phthalide product **95a** in 57% yield and moderate enantioselectivity (70% ee) (Scheme 19).[67] The authors noted that only the cationic iridium complex catalyzes the reaction, and no reactivity was observed employing a neutral iridium catalyst. Recently, the same group reported further studies of this transformation. The new catalytic system involves the (*R*)-SEGPHOS as ligand, which enables the conversion of a wide range of 2-ketobenzaldehydes to the corresponding phthalides **95** in moderate yields (23−71%) and good to high enantioselectivities (74−98% ee).[68] The authors proposed a mechanism analogous to that of previously reported rhodium[69] and cobalt[70] systems, which commences with the oxidative addition of the aldehydic C−H bond to form iridium hydride species **96**. Migratory insertion and subsequent C−O bond-forming reductive elimination leads to the formation of the product. The KIE of 1.14 indicated that the C−H activation step is not the turnover-limiting step of this process.

2.1.2. Functionalization of C(sp^3)−H Bonds. Enantioselective functionalization of C(sp^3)−H bonds is a particularly challenging task.[71] C(sp^3)−H bonds are typically stronger than the C(sp^2)−H bonds. Moreover, the ubiquity of aliphatic C−H bonds in organic molecules and their similar dissociation energies make the control of chemo-, regio-, and stereoselectivities very difficult. Several examples, which involve the

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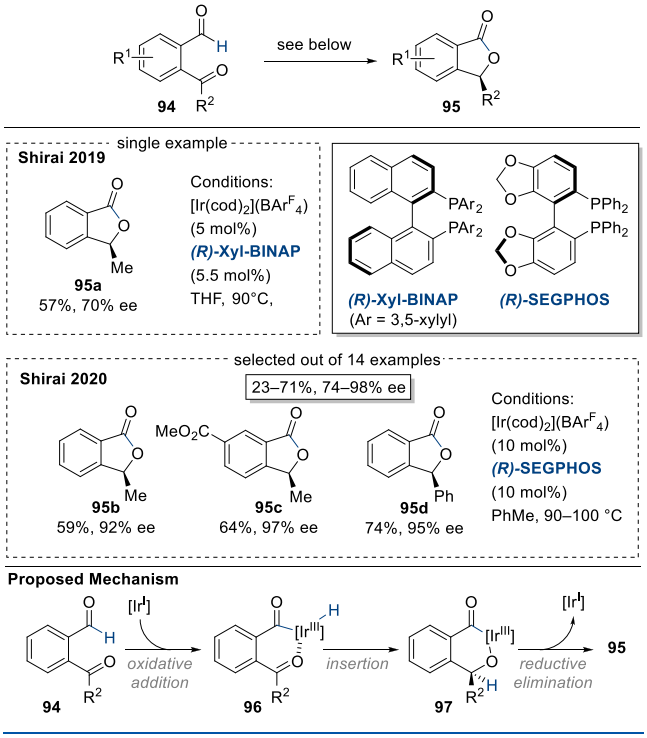
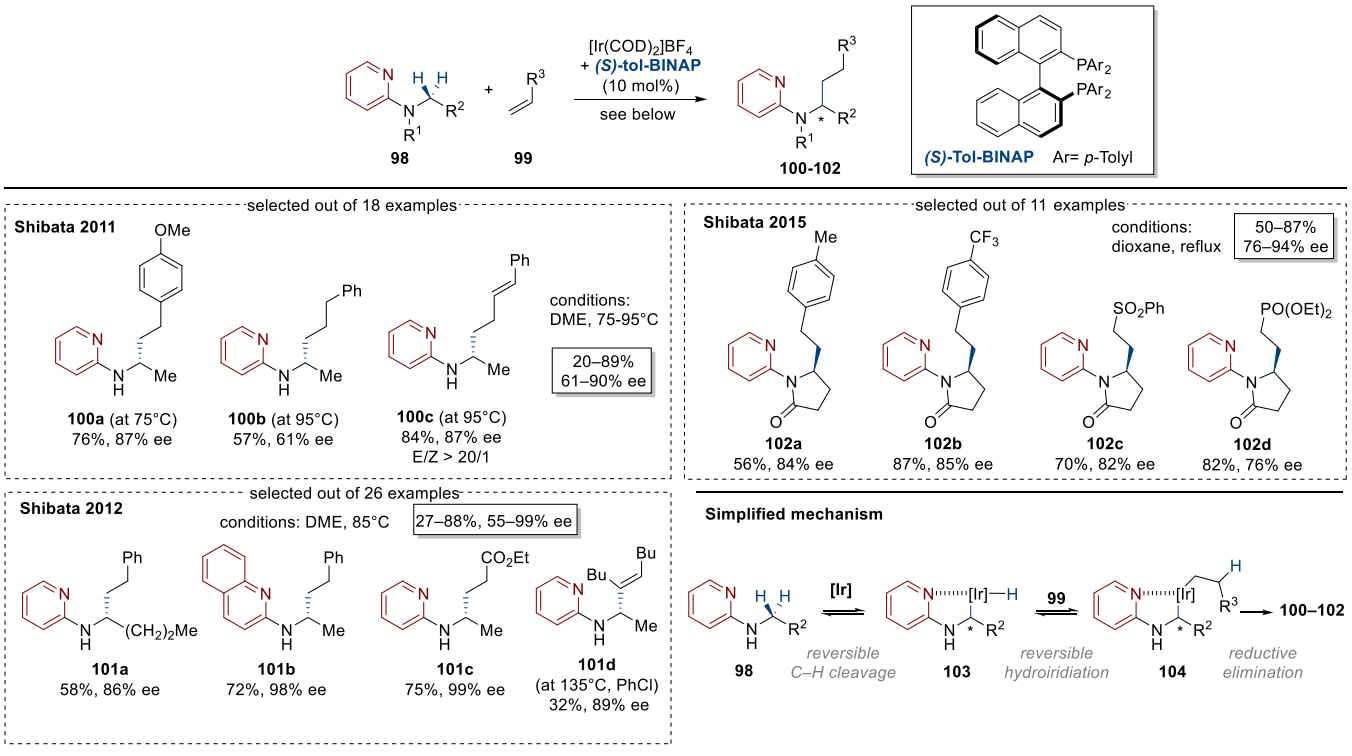
Scheme 19. Enantioselective Intramolecular Hydroacylation of 2-Ketobenzaldehydes



activation of C(sp^3)–H bonds through the oxidative addition to the iridium(I) center, have been disclosed.

The Shibata group explored the Ir(I)/Ir(III) catalytic system for enantioselective functionalization of C(sp^3)–H bonds in 2-(alkylamino)pyridines with styrenes (Scheme 20).[72] Various styrene derivatives were competent substrates, affording the corresponding products in moderate to high yields (56–89%) and good enantioselectivities (84–90% ee). Allylbenzene and conjugated 1-phenyl-buta-1,3-diene were also found to be suitable partners, however giving products **100b** and **100c** with moderate (61% ee) and good (87% ee) enantiomeric excesses, respectively. Soon after, the same group further examined the scope of this reaction.[73] The authors explored the effect of alkyl substituents on the nitrogen atom (*e.g.* **101a**). Functionalization of the C–H bonds of the alkyl chain, with lengths up to *n*-pentyl, was achieved in moderate to good yields (58–76%) and good enantiomeric excesses (83–88% ee). The authors further examined different heteroaromatic directing groups, which indicated that only pyridine derivatives efficiently drive this transformation. Finally, the reaction was assessed with different alkene acceptors, such as acrylates, or vinyl- and allyl-silanes that gave the alkylated products in modest to high yields (27–88%) and moderate to excellent enantioselectivities (61–99% ee). Additionally, 5-decyne was a competent acceptor, affording **101d** in 89% ee, albeit with modest yield (32%). The Shibata group further developed this methodology for the enantioselective C(sp^3)–H alkylation of γ-butyrolactams.[74] A variety of styrenes proved as successful coupling partners, giving the products in moderate to high yields (50–87%) and high enantioselectivities (82–94% ee) (Scheme 20). Acrylates, sulfonates and phosphonates were also well tolerated, affording the alkylated product in good to high yields (70–87%) and high enantiomeric excesses (76–94% ee). The authors suggest that the reaction is initiated with a C(sp^3)–H bond cleavage by the iridium(I) catalyst, thereby generating the intermediate **103**, bearing a chiral tertiary carbon atom. The subsequent hydrometalation of the incoming alkene furnishes the intermediate **104**, whereupon reductive elimination affords the product (Scheme 20). The alternative pathway following the modified Chalk–Harrod mechanism has not been excluded.

Scheme 20. Pyridine Directed Enantioselective Functionalization of C(sp^3)–H Bonds



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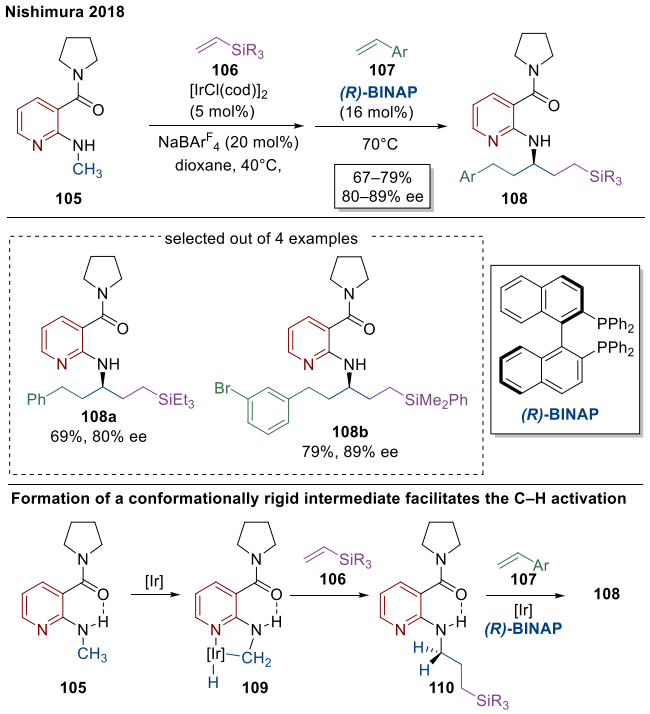
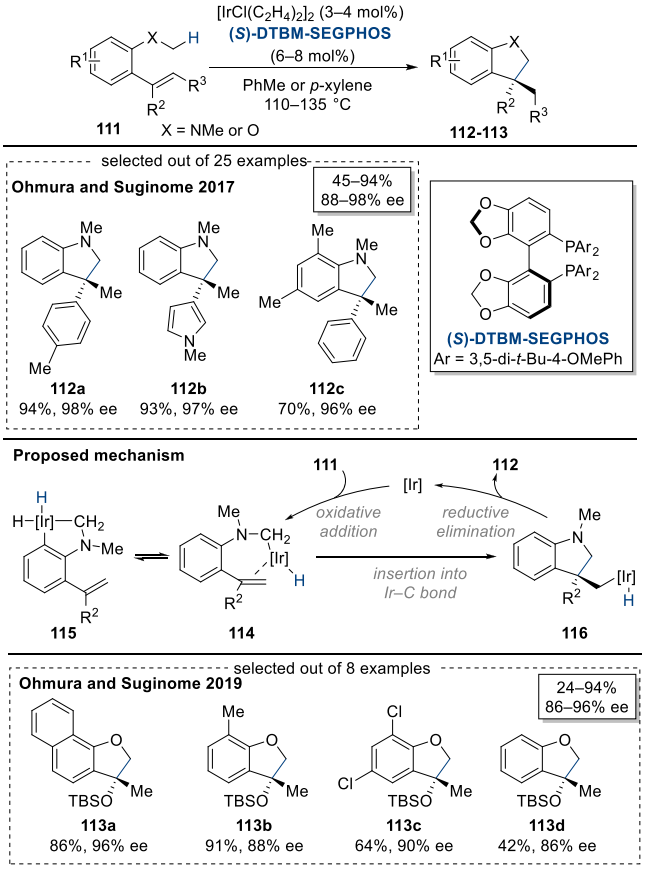
In 2018, Nishimura disclosed a protocol that allows for the enantioselective sequential alkylation of the *N*-methyl group of pyridine derivatives **105** using an iridium(I) complex in the presence of a chiral phosphine ligand (Scheme 21).[75] This strategy enables the double functionalization of the *N*-methyl group with two different alkanes, added sequentially in a one-pot process. The second, enantioselective functionalization is controlled by the (*R*)-BINAP ligand to give chiral α-substituted amines **108** in good yields (67−79%) and good enantioselectivities (80−89% ee). The authors noted the necessity of using vinylsilanes **106** for the first alkylation, as it would ensure selective monoalkylation under milder reaction conditions. As for the second alkylation, only examples with styrene and 3-bromostyrene were reported. The reaction requires an amide substituent on the C3-position of the pyridine. This indicates the importance of an intramolecular hydrogen bond interaction between the amine and N−H groups, which provides a conformational constraint to orient the alkyl group close to the iridium center.[76]

Scheme 21. Enantioselective Sequential Functionalization of C(sp^3)−H Bonds



In 2017, Ohmura and Suginome reported a highly enantioselective cycloisomerization of *N*-methylanilines bearing *o*-alkenyl groups **111** to form indolines (Scheme 22).[77] The catalytic system involves an iridium(I) complex, bearing the chiral bidentate phosphine ligand (*S*)-DTBM-SEGPHOS, which converts a wide range of *o*-alkenyl-*N*-methylaniline substrates with various substitution patterns on the aromatic ring, as well as the double bond, giving rise to products **112** with high yields (45−94%) and high enantiomeric excesses (88−98% ee). The KIE of 3.3 indicates that the C−H oxidative addition is the rate-limiting step. Based on this result, and deuterium labeling experiments, the authors proposed the mechanism for the transformation, which commences with a rate-determining C−H activation of the *N*-methyl C(sp^3)−H bond to form the iridium hydride **114**, which exists in equilibrium with a nonproductive iridacycle **115**. The subsequent insertion of the C=C bond into the Ir−C bond within **114**, in a 5-*exo* fashion, leads to iridium hydride **116**, which converts to the product upon the C−H bond-forming reductive elimination. In 2019, the same group further expanded this methodology to the synthesis of enantioenriched 2,3-dihydrobenzofurans **113**.[78] The intramolecular functionalization of *O*-methyl C(sp^3)−H bonds was achieved employing the same catalyst ligand system as for the cycloisomerization of *N*-methylanilines discussed above, which furnished the 2,3-dihydrobenzofuran products **113** in yields ranging from 24% to 94% and high enantioselectivities (86−96% ee).

Scheme 22. Asymmetric Addition of *N*- and *O*-Methyl C(sp^3)−H Bonds across C=C Bonds



2.2. C−H Oxidative Addition to Iridium(III) Complexes

2.2.1. C−H Borylation. In addition to the aforementioned Ir(I)/Ir(III) catalysis, a different C−H functionalization pathway, via an Ir(III)/Ir(V) catalytic cycle, has been disclosed. In this context, the iridium-catalyzed C−H borylation presents as one of the most remarkable examples. Owing to their low toxicity and high stability, aryl- and alkylboronate esters are highly relevant building blocks for C−C and C−X bond formation.[79] The use of C−H functionalization methodologies allows for a more convenient access to these compounds, as they can be obtained directly from the corresponding arenes or alkenes under mild conditions, without the need for forming highly sensitive organolithium or organomagnesium intermediates from organic halides.[80] The C−H activation step of the iridium catalyzed borylations is mechanistically interesting. Theoretical studies performed by Sakaki[29] on one of the early examples of iridium catalyzed C−H borylation processes[81]

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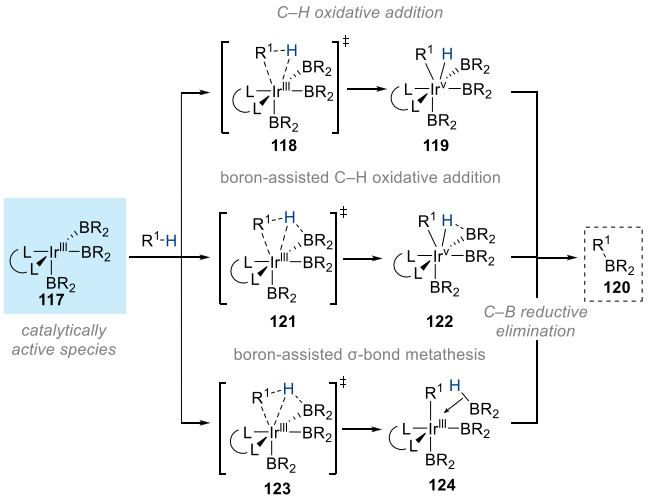
indicated the iridium(III) tris-boryl complex **117** (Scheme 23) as a catalytically active species, which activates arene C−H

Scheme 23. Proposed C−H Activation Mechanisms of the Ir-Catalyzed Borylation Processes

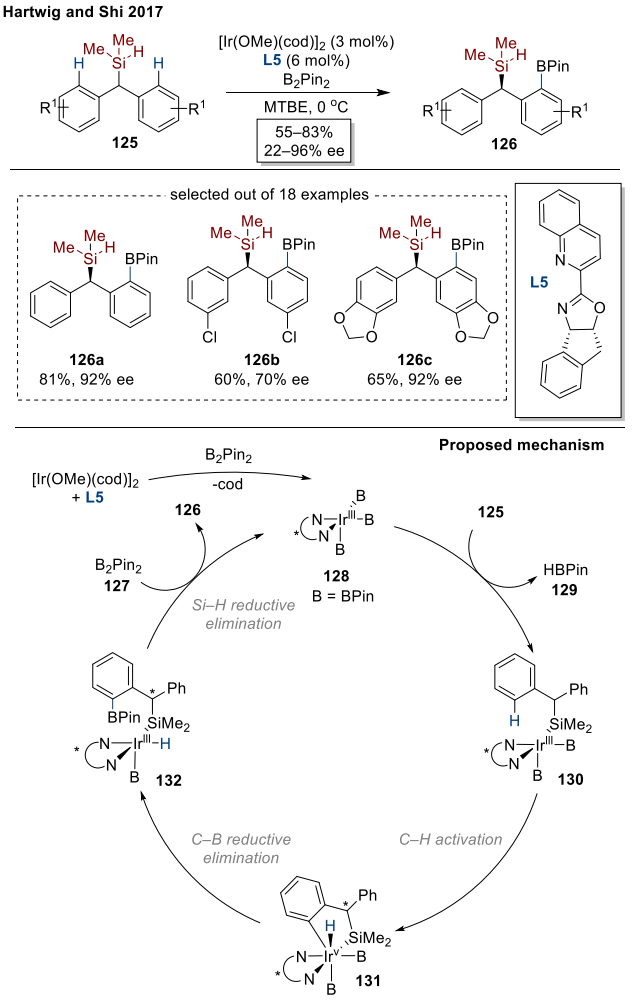


bonds through the oxidative addition mechanism leading to a hexacoordinated iridium(V) hydride species **119**. Mechanistic investigations of different C−H borylation processes suggested a similar activation pathway, however involving the assistance of a boron ligand during the C−H oxidative addition. This indicates the importance of the attractive interaction between the empty *p*-orbital of the boron and the hydride.[82,83] An alternative mechanism involving a boron assisted σ-bond metathesis has also been considered.[84,85]

The first example of an enantioselective iridium catalyzed C−H borylation was reported by Hartwig and Shi and co-workers in 2017 (Scheme 24).[86] Previously, Hartwig's group reported silyl-directed C−H borylation where planar bipyridine and phenanthroline ligands provide the best performance.[87] Taking inspiration from this, the authors developed a closely related chiral analog of bipyridine, namely quinolyl oxazoline ligand **L5** which enabled the enantioselective borylation of diarylmethylsilanes **125** with good yields (55−83%) and enantioselectivities (22−96% ee). The silyl group selectively directs the borylation to the *ortho* C−H bond of the aromatic ring. The reaction proceeds readily with a wide range of substituents in the *meta*- and *para*-positions of the aromatic rings, while the presence of an *ortho*-substituent is less tolerated. Based on the aforementioned analogous nonenantioselective iridium catalyzed borylation,[87] the reaction commences with the formation of the active iridium(III)-tris-boryl catalyst **128**. Next, the substrate **125** binds to the metal center with a concomitant elimination of HBPin, generating iridium(III) species **130**. The subsequent C−H activation yields the iridium(V) metallacycle **131**. The C−B bond forming reductive elimination provides intermediate **132**, which upon reacting with a molecule of B_2Pin_2 releases the product and regenerates the active catalyst **128**.

In 2019, Xu and co-workers reported an enantioselective borylation of diarylmethylamines (Scheme 25).[88] In contrast to the previous report, using silane as a relay directing group, the amine directed C−H borylation requires two vacant coordination sites, one for the directing group and the other for C−H cleavage.[89] In order to address this issue, the authors developed a family of readily available chiral *B,N*-ligands (*e.g.* **L6**−**L7**). This

Scheme 24. Enantioselective Borylation of Aromatic C−H Bonds Directed by Silanes



catalytic system was applied for desymmetrization of diarylmethylamines **133** to deliver the boron containing products **134** with good to excellent yields (60−95%) and enantioselectivities (79−96%). The substrates bearing electron-withdrawing groups afford the corresponding products in higher enantiomeric excesses than those with electron-donating substituents. The scope of the amino group is mostly limited to *N,N*-dimethyl compounds, as even a slight increase of steric bulk at the nitrogen atom dramatically reduces the yield. This strategy is also effective for kinetic resolution of racemic diarylmethylamines. In this case, the chiral ligand **L7** enables the borylation of various racemic substrates with moderate to good conversion (24−54%, s = 9−68) and high enantiomeric excesses (72−94% ee). Several catalytic pathways were evaluated computationally. The most favored mechanism involves a boron assisted oxidative addition to the iridium(III) center, followed by isomerization of the borane-bridged hydride **138**. A subsequent C−B bond formation yields the desired product, and the catalyst is reactivated by reacting with another molecule of B_2Pin_2.

The same group has further applied the new chiral *B,N*-ligands in an enantioselective amide directed borylation of cyclopropanes (Scheme 26).[90] A catalytic amount of iridium(I) precursor, in the presence of the ligand **L8**, allowed for the borylation of a wide range of cyclopropanes **141** in moderate to

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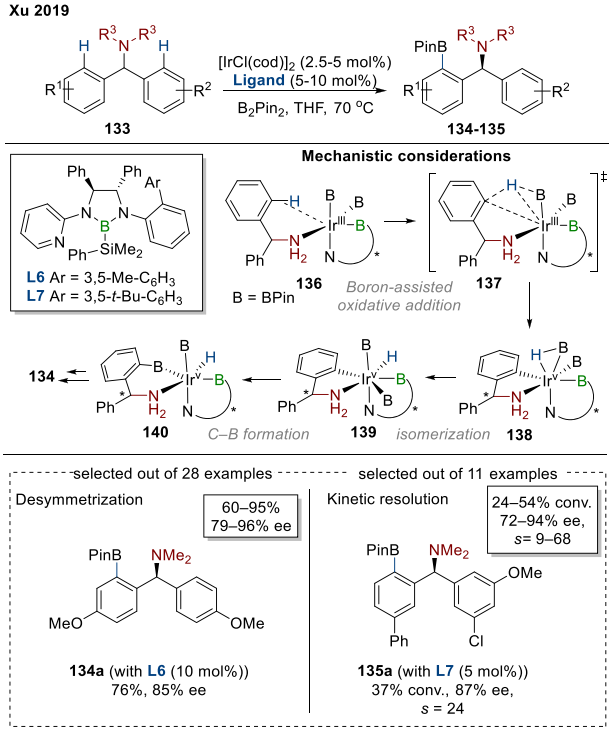
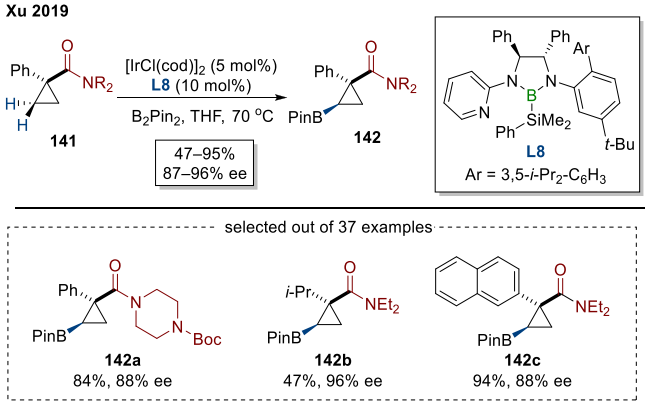
Scheme 25. Enantioselective Borylation of Diarylmethylamines



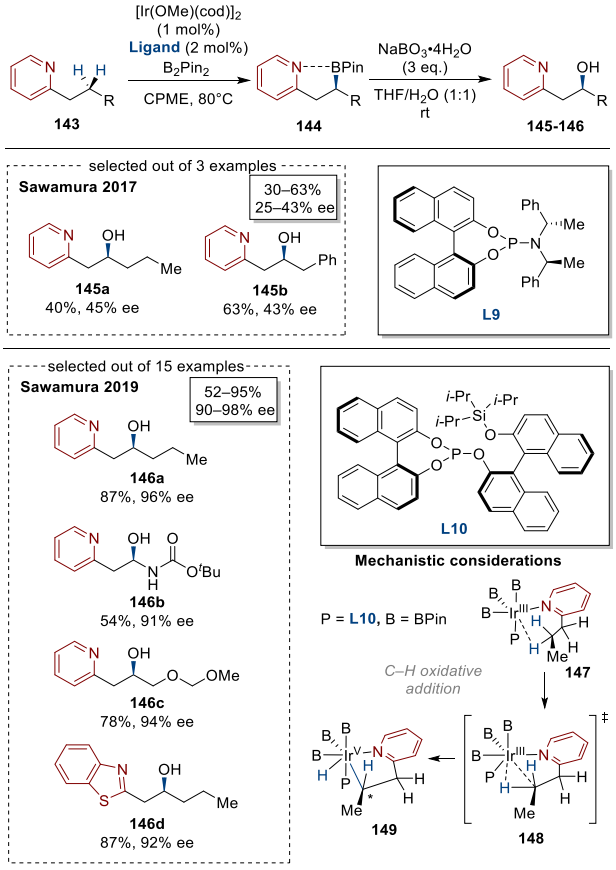
Scheme 26. Ir-Catalyzed Asymmetric C−H Borylation of Cyclopropanes



excellent yields (47−95%) and excellent enantioselectivities (87−96%). Notably, this reaction provides the products as single regio- and diastereomers. The application of the iridium catalyst suppresses the undesirable cyclopropane ring-opening side reaction, which is frequently observed in palladium-catalyzed C−H borylations.[91] The reaction scope tolerates a wide range of substituents, including various amide groups, electron-rich and electron-poor arylcyclopropanes, as well as alkyl-substituted compounds. The boronate ester functionality can be used for further derivatizations orthogonal to the directing group and proceed without erosion of enantiomeric excess. During the revision of this manuscript, Xu and co-workers disclosed enantioselective α-C(sp^3)−H borylation of azacycles employing their chiral bidentate boryl ligands.[92]

The first example of an enantioselective iridium-catalyzed borylation of C(sp^3)−H bonds was reported by Sawamura and co-workers in 2017 (Scheme 27). This work is based on their

Scheme 27. Enantioselective Borylation of C(sp^3)−H Bonds



previously reported racemic rhodium-catalyzed borylation of *N*-adjacent C(sp^3)−H bonds with a silica supported triarylphosphine ligand.[93] Efforts toward the development of a highly enantioselective variant of this process led to a chiral phosphoramidite ligand **L9**.[94] The alcohol products **145**, formed upon oxidation of the corresponding alkylboronates, were obtained with moderate yields (30−63%), but with low enantiomeric excesses (25−43% ee). Soon after, the same group developed a new chiral phosphite ligand **L10**, which enables this process in a highly enantioselective fashion (52−95% yield, 90−98% ee).[95] Heterocycles other than pyridine, such as benzimidazole, benzothiazole, and benzoxazole, are competent directing groups. Various functional groups at the alkyl chain of the substrate are also well tolerated. Using the monodentate ligand is crucial to providing the two coordination sites required for the heteroaryl directed C−H activation. Quantum chemical calculations suggest that the monophosphite-Ir-tris(boryl) complex **147** provides a narrow chiral reaction pocket, where the activation of the enantiotopic C−H bond is governed by multiple noncovalent interactions. The lowest energy conformers of the *P,N*-coordinated precursor iridium complex **148** exhibit agostic interaction between the pro-*S* hydrogen atom and the iridium(III) center prior to the C−H bond cleavage, which occurs via direct oxidative addition, yielding the corresponding Ir(V) hydride **149**.

Recently, Phipps and co-workers demonstrated a conceptually different strategy to control enantioselective C−H borylation processes (Scheme 28).[96] In contrast to the examples by Hartwig, Shi, and Xu described above (Schemes 24−26), where the chiral information is covalently incorporated into the ligand scaffold, the authors employed **L11**, a sulfonate

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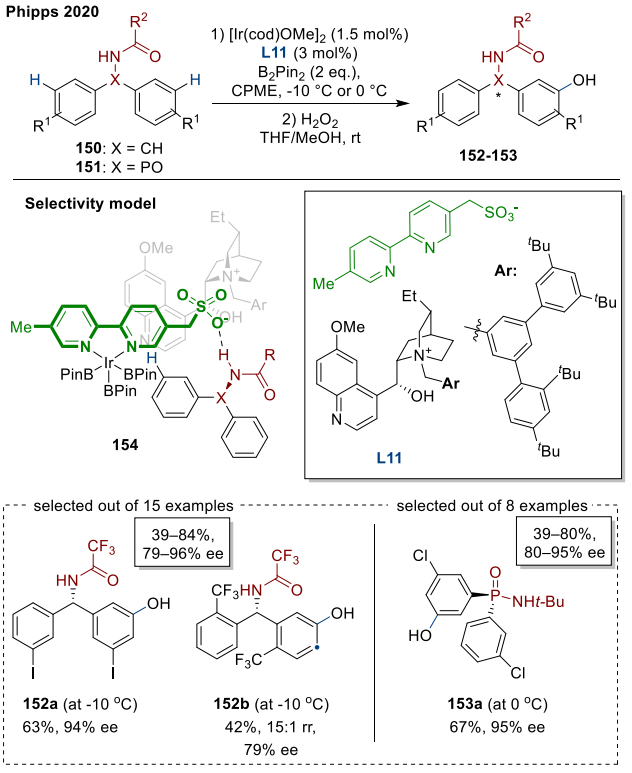
Scheme 28. Enantioselective Remote C−H Borylation Directed by a Chiral Cation

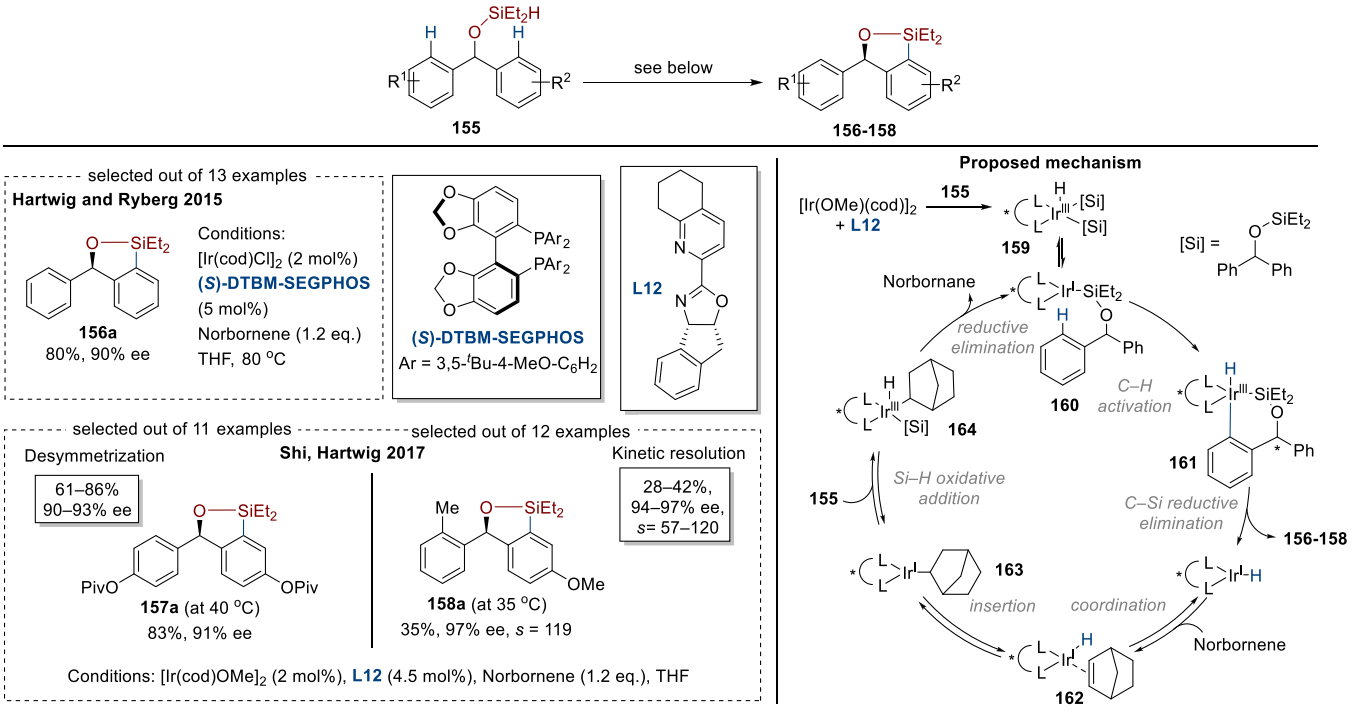


containing anionic bipyridine ligand, paired with a chiral cation derived from quinine. This new strategy enables a long-range asymmetric induction in the functionalization of enantiotopic C−H bonds, located in a remote position from the newly formed stereogenic center. The authors developed an enantioselective *meta*-borylation of benzhydrylamides **150** and diaryl phosphinamides **151**. The sulfonate bearing bipyridine ligand imparts a *meta*-selectivity over an *ortho*-functionalization, which is attributed to the directing effect of a hydrogen bond interaction between the substrate and the sulfonate group.[97] The chiral cation induces enantioselectivity, which is a unique and largely unexplored approach to enantioselective transition metal catalysis.[98,99] This transformation provides the chiral phenol products **152−153**, formed upon oxidation of the boronate intermediate, with good yields (39−84%) and high enantioselectivities (79−96% ee), as well as excellent *meta*-selectivities (up to >20:1 rr).

2.2.2. C−H Silylation. In addition to the borylation reactions, the iridium-catalyzed functionalization of C−H bonds with silanes represents an important example of processes involving the shuttling between Ir(III)/Ir(V) oxidations states in the catalytic cycle.[100] The C−H activation approach offers a straightforward pathway to the corresponding silylation products,[101] which can be employed in a wide range of cross-couplings[102] and oxidative derivatizations[103] or as monomers for important polymers.[104] Despite significant advances in the development of iridium catalyzed C−H silylation reactions, enantioselective variants of these methodologies have only recently surfaced.

The first example of an enantioselective silylation of aromatic C−H bonds was reported by Hartwig, Ryberg, and co-workers in 2015 (Scheme 29).[105] The authors demonstrated that a catalyst generated from an iridium(I) complex with the chiral (*S*)-DTBM-SEGPHOS as ligand enables an intramolecular silylation, giving rise to product **156a** in 80% yield and 90% ee. This protocol, however, suffered from the limited scope and required relatively high reaction temperatures; thus, the authors addressed these shortcomings employing rhodium catalysis. A few years later, the iridium-based catalytic system was further developed by the groups around Shi and Hartwig.[106] The authors evaluated a wide range of chiral bidentate and tridentate

Scheme 29. Enantioselective Intramolecular Silylation of Aromatic C−H Bonds



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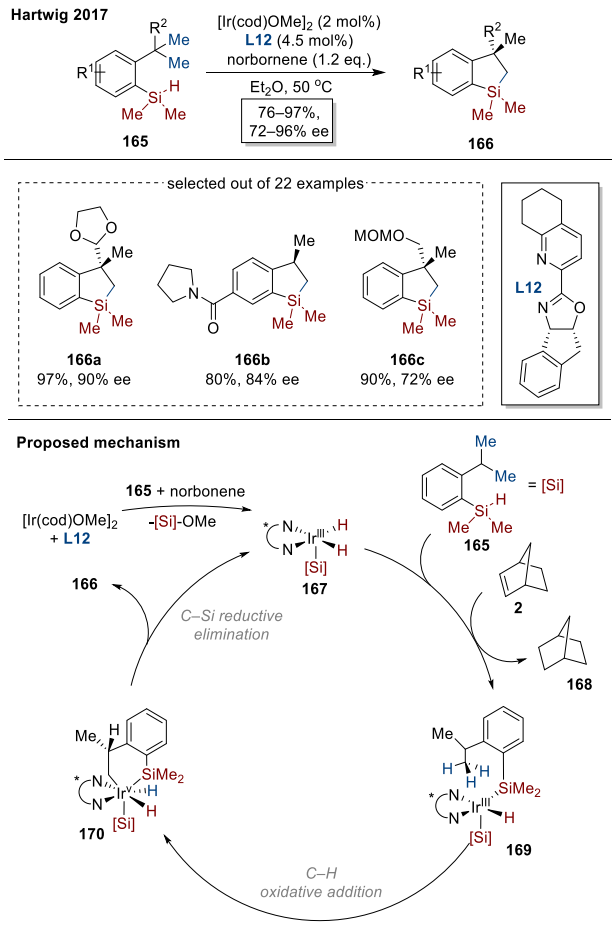
nitrogen ligands, of which a partially hydrogenated quinolinyl oxazoline **L12** performed best. This enabled the desymmetrization of a broad scope of *meta*- and *para*-substituted diarylmethanol derivatives, bearing both electron-rich and electron-poor moieties in good yields (61−86%) and high enantioselectivities (90−93%). The kinetic resolution of unsymmetrical substrates furnished the enantioenriched diarylmethanols **158**, bearing two different *ortho*-substituted aryl groups, with moderate to good yields (28−42%) and high enantiomeric excesses (94−97% ee). Preliminary mechanistic studies indicated that the C−H activation is irreversible and occurs after the rate-limiting step. The norbornene acts as a sacrificial hydrogen acceptor and the C−H bond-forming reductive elimination to form norbornane is the rate-determining step. The proposed catalytic cycle involves Ir(I)/Ir(III) intermediates. Later studies of iridium catalyzed silylation processes, however, suggest that the C−H oxidative addition of C−H bonds to the iridium(III) center is operative in various catalytic systems;[107,108] therefore, we located the aforementioned example in this section.

Hartwig and co-workers disclosed the first example of an enantioselective C(sp^3)−H silylation catalyzed by iridium complexes.[109] The tetrahydroquinoline-based ligand **L12** enabled the silylation of unactivated methyl groups, leading to products **166** with good to excellent yields (76−97%) and high enantioselectivities (72−96% ee) (Scheme 30). The reaction tolerates a wide range of substituents, including tertiary amine,

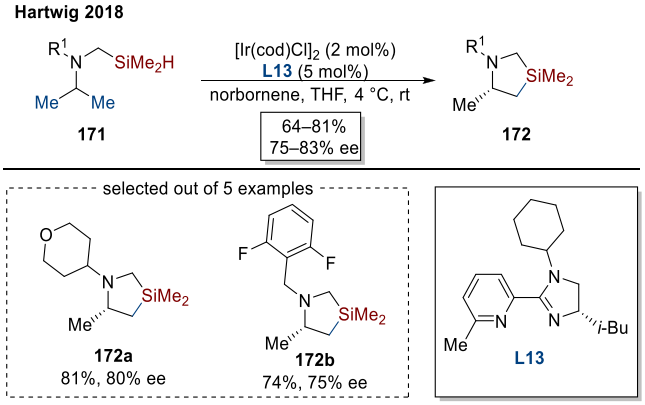
Scheme 30. Enantioselective Intramolecular Silylation of C(sp^3)−H Bonds



amides, silyl ethers, or carbonates and allows for the synthesis of organosilanes **166**, bearing quaternary stereogenic centers, in high enantioselectivity. Computational studies performed by Huang[108] and co-workers suggest that this reaction proceeds through a Ir(III)/Ir(V) catalytic cycle, which is initiated by the formation of the iridium(III) silyl dihydride active species **167**. The subsequent migratory insertion with the norbornene, followed by a transmetalation with the substrate **165**, leads to the iridium(III) complex **169**. Next, oxidative addition to the C(sp^3)−H bond furnishes a hexacoordinate iridium(V) species **170**, which upon the C−Si bond forming reductive elimination, produces the product **166** and regenerates the active catalyst.

Hartwig and co-workers further developed the enantioselective methodology for the silylation of C(sp^3)−H bonds. The authors reported the procedure to convert aliphatic amines **171** into silapyrrolidines **172** by a selective functionalization of C−H bonds β to the nitrogen (Scheme 31).[110] Notably, the activation

Scheme 31. Enantioselective and β-Selective C(sp^3)−H Silylation of Aliphatic Amines



of the β-C−H bonds of aliphatic amines is particularly challenging. Typically, amines direct the reagent or catalyst to activate more distal γ- and δ-C−H bonds through 5- or 6-membered metallacycles.[111] Moreover, the C−H bonds α to nitrogen are weaker than those at the β-position. The desired β-selectivity was achieved by linking a hydrosilyl group to the nitrogen via a methylene bridge. The development of the enantioselective variant led to the design of imidazoline-based chiral ligand **L13**, which features a greater basicity than the previously used oxazoline scaffold. The authors proposed that the imidazoline ligand would deliver a more electron-rich catalyst, facilitating the C−H oxidative addition. As a result, the asymmetric C−H silylation process was achieved at low temperature with good yields (64−81%) and moderate enantiomeric excesses (75−83% ee).

2.3. C−H Activation via CMD Mechanism

Iridium(III) complexes can activate C−H bonds in a non-oxidative pathway through the CMD process. This C−H bond activation mechanism is operative in the functionalization of phosphine oxides by iridium(III) complexes bearing cyclopentadienyl type ligand in the presence of a carboxylic acid additive. Studies reported by Chang and co-workers on a C−H amidation process demonstrated that the carboxylic acid is involved in the C−H bond cleavage (Scheme 32).[112] The use of enantiopure acid **177** served as a mechanistic probe, indicating the influence of the chiral acid on the enantiodetermining C−H activation step promoted by the achiral iridium(III) complex

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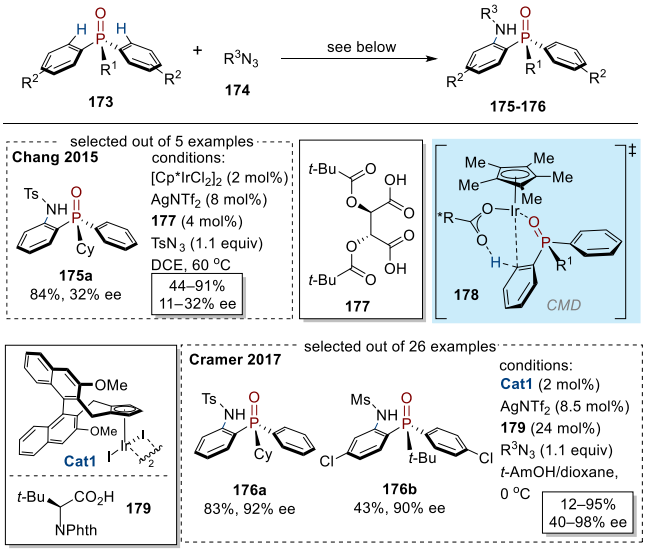
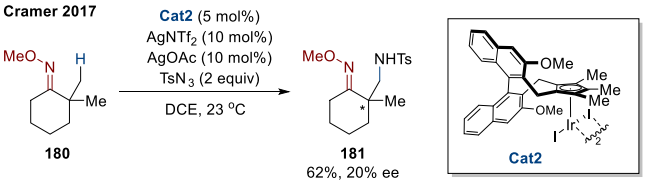
Scheme 32. Enantioselective C−H Amidation of Phosphine Oxides



$[Cp^*IrCl_2)]_2$ (Cp*- pentamethyl cyclopentadienyl). The products bearing phosphorus stereocenters[113] **175** were obtained with good yields (44−91%) and low enantioselectivities (11−32% ee). In 2017, Cramer and co-workers developed a catalytic system for a highly enantioselective C−H amidation of phosphine oxides.[114] The reaction is catalyzed by chiral iridium complex **Cat1**,[115] equipped with Cramer's chiral cyclopentadienyl (Cp^x) ligand,[116] in the presence of a (*S*)-*tert*-leucine derivative **179**. The authors observed a very strong cooperative effect between the Cp^x ligand and the chiral acid **179**, which influences both the yield and enantioselectivity of the process. The matched combination of the ligand and **179** allow for the preparation of the C−H amidation products **176** with good yields (12−95%) and moderate to high enantioselectivities (40−98% ee). In contrast, the mismatched combination employing (*R*)-*tert*-leucine derivative and **CAt1** affords product **176a** with only 15% yield and 20% ee. This indicates that the synergistic effect between the two chirality sources enhances the transmission of chiral information to the substrate as well as facilitating the process.

In the same year, a promising preliminary example of the enantioselective amidation of C(sp^3)−H bonds was reported (Scheme 33).[117] The iridium complex **Cat2**, bearing a

Scheme 33. Enantioselective Amidation of C(sp^3)−H Bonds



pentasubstituted Cp^x ligand, delivers the amidated oxime **181** with 62% yield, however with low enantiomeric excess (20% ee). Although further optimization is needed, this result indicated the potential of the iridium Cp^x complexes to control the enantioselectivity of this challenging transformation.

Cramer's group further developed the enantioselective C−H functionalization of phosphine oxides **173**, employing their catalytic system, which relies on the cooperative action of the chiral iridium complex **Cat1** with the chiral acid **179**. In 2018, the authors reported the enantioselective arylation of phosphine oxides with *o*-quinone diazides, yielding products **183**−**185**, which possess one or two stereogenic elements, namely a phosphorus stereocenter and a chiral axis (Scheme 34).[118−122] Employing *o*-quinone diazides lacking a substituent at the C5 position gives products **183**, bearing only the steregenic center at the phosphorus atom with high yields (41−98%) and enantioselectivities (71−97% ee). Diazo reactants with increased bulk at the C5 position generate arylated phosphinoxides **185** with a stable chiral axis in addition to the chiral phosphorus, with yields ranging from 59% to 96% and up to high stereoselectivities (1.1:1−20:1 dr, 36−99% ee). This strategy also enables the synthesis of purely axial phosphinoxides **185** with good yields (53−95%) and high enantiomeric excesses (89−92% ee). Facile recrystallization of **185a** gives the product in an enantiopure form. A two-step transformation of the chiral phosphine oxide products gives access to monodentate chiral phosphorus(III) compounds **186**−**188**, which possess structural elements with proven importance as ligands in asymmetric catalysis.[122]

The mechanism of the enantioselective C−H functionalization of phosphine oxides starts with the generation of the dicationic iridium complex **189** by iodine abstraction from the dimeric complex ($[IrCp^xI_2]_2$) with a silver(I) salt (Scheme 35). In the presence of the acid, the dicationic complex **189** exists in equilibrium with the monocationic carboxylate complex **190**. Subsequent coordination of the phosphine oxide to the iridium center, followed by the enantiodetermining cyclometalation step through the CMD mechanism forms the iridacycle **191**. The amidation reaction proceeds with the coordination of the azide **174**, followed by a migratory insertion, which leads to the formation of species **193**. The subsequent protodemetalation delivers the product and regenerates the active catalytic species **190**. The arylation process involves the reaction of the diazo reagent **182a** with the iridacycle **191** to form the iridium carbenoid **194**, which undergoes migratory insertion to generate the iridium enolate complex **195**. The protodemetalation by the chiral acid yields the product. Notably, the enantiodetermining step of the C−H arylation process leading to products **184**, which has a chiral axis as a sole stereogenic element, differs from the transformations giving *P*-chiral products and occurs after the C−H activation step.

During the revision of this manuscript, two reports of enantioselective C−H functionalizations catalyzed by achiral iridium cyclopentadienyl complexes in the presence of chiral acid cocatalysts were disclosed.[123,124]

3. OUTER-SPHERE C−H FUNCTIONALIZATION

In the outer-sphere C−H functionalization, the metal does not directly interact with the activated C−H bond.[23,24] Instead, it involves reaction of the ligand with the C−H bond or a hydrogen atom transfer (HAT). These include C−H functionalizations by iridium-carbenoid, -nitrenoid, or -oxo species proceeding via the HAT, followed by a radical rebound mechanism (Scheme 36a) or by a concerted insertion pathway (Scheme 36b).[125,126] The enantioselective C−H functionalization processes involve forging new C−C or C−N bonds by chiral iridium-carbenoids or -nitrenoids, respectively.

3.1. Reactions of Iridium Carbenoids

Enantioselective metal carbenoid C−H insertions are largely dominated by rhodium and copper catalysis;[127,128] however,

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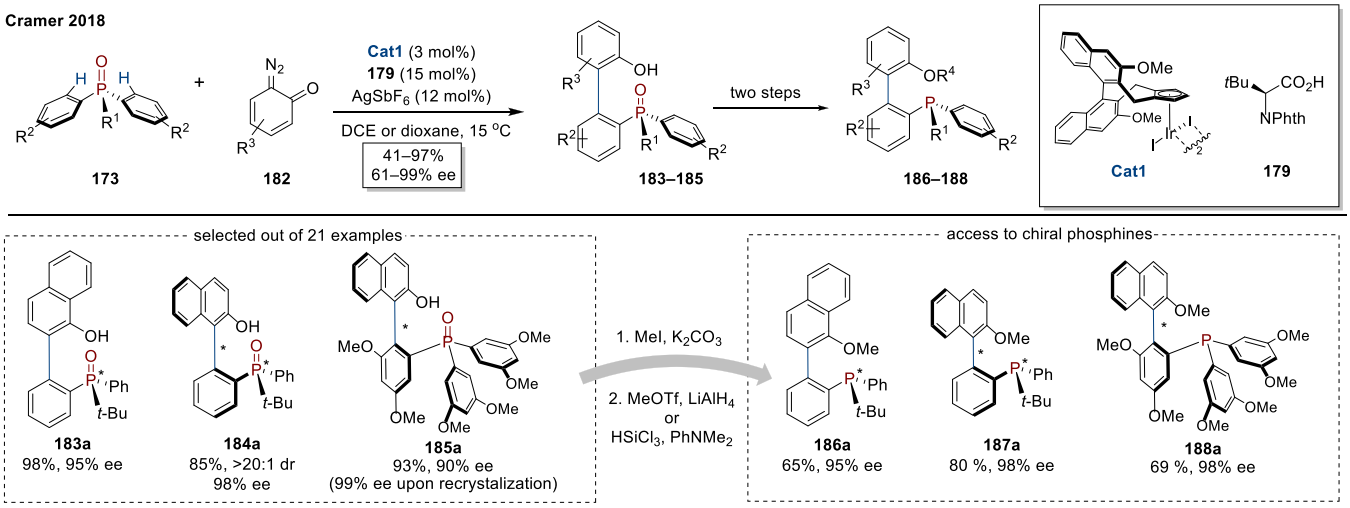
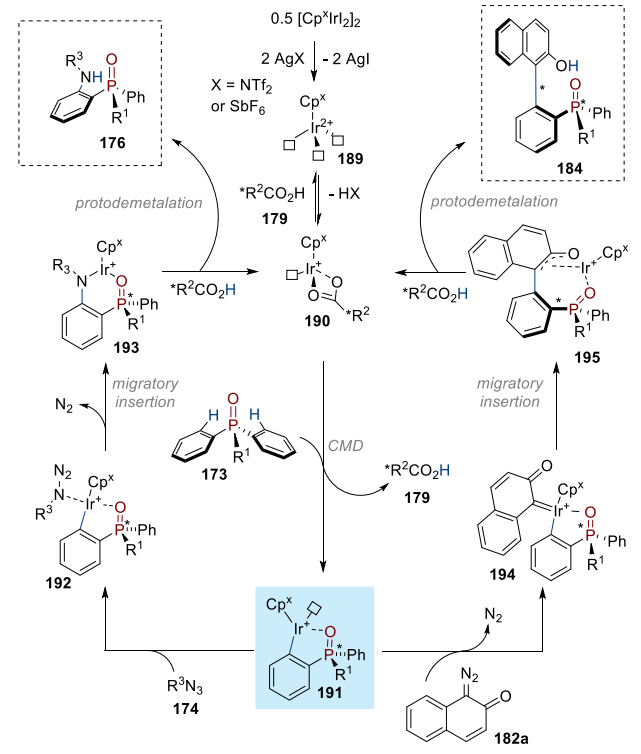
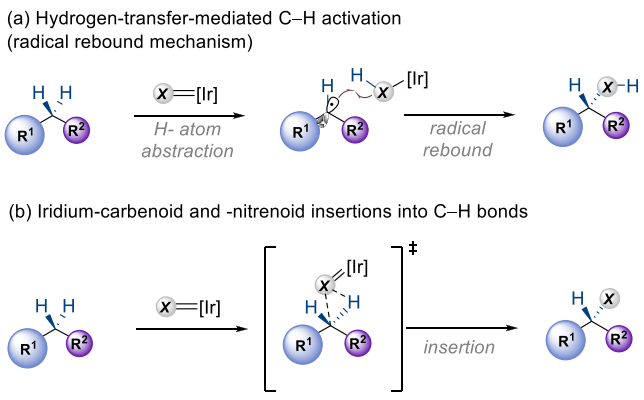
Scheme 34. Enantioselective C−H Arylation of Phosphine Oxides



Scheme 35. Proposed Mechanism of the Enantioselective C−H Functionalization of Phosphine Oxides



Scheme 36. General Mechanisms of Iridium-Catalyzed Outer-Sphere Functionalization of C−H Bonds: (a) Radical Mechanism through HA;, b) Direct Ligand Insertion into C−H Bonds



over the last ten years, iridium chemistry has also brought an important contribution to this area. In 2009, Katsuki and co-workers introduced the first example of a catalytic enantioselective iridium carbenoid C−H insertion (Scheme 37).[129] This report demonstrated the ability of Ir(III)(salen) catalysts **Cat3** and **Cat4** to promote highly stereoselective C−H insertions of α-aryl-α-diazoacetates and α-diazopropionates into THF and cyclohexadiene at low temperatures (up to −60 °C). The reaction with THF is highly *syn* selective and tolerates various aryl substitution patterns on the diazoester substrate. Reactions with the cyclohexadiene selectively give the C−H insertion products without the undesired cyclopropanation process.[130] The chiral cyclohexadiene derivatives **200** were obtained with good yields (53−95%) and high enantioselectivities (83−99% ee). Remarkably, α-alkyl-α-diazoacetates, which tend to undergo competing β-hydride elimination,[131] effectively yield the desired products **200c** and **200d** with high enantiomeric excesses (83% ee and 99% ee, respectively).

The potential of iridium carbenoid insertions into the C(sp^3)−H bond aroused the interest in the community and was further explored toward the development of new catalytic systems. In 2012, Che and co-workers reported the first iridium porphyrin, built on a D_4-symmetric Halterman porphyrin,[132] which catalyzes the carbenoid C−H insertions into both THF and cyclohexadiene with high to excellent diastereo- and enantioselectivities (2.5:1−20:1 dr, 86−98% ee), along with high turnover numbers (Scheme 38).[133] A variety of methyl-α-aryl-diazoacetate substrates **202** cleanly converts into the C−H insertion products **203**−**204** in the presence of 1 mol % of the catalyst **Cat5** at −40 °C. The reactivity of α-alkyl-α-diazoacetates, however, has not been reported employing this catalytic system. Notably, the ruthenium analog of the catalyst does not promote the C−H insertion process demonstrating the advantage of the iridium system. With respect to the scope, the electronic properties of the aryl moiety did not have a substantial effect on the formation of the products. Both electron-withdrawing and -donating substituents were tolerated, as well as naphthalene and heteroaromatic thienyl rings. The reaction

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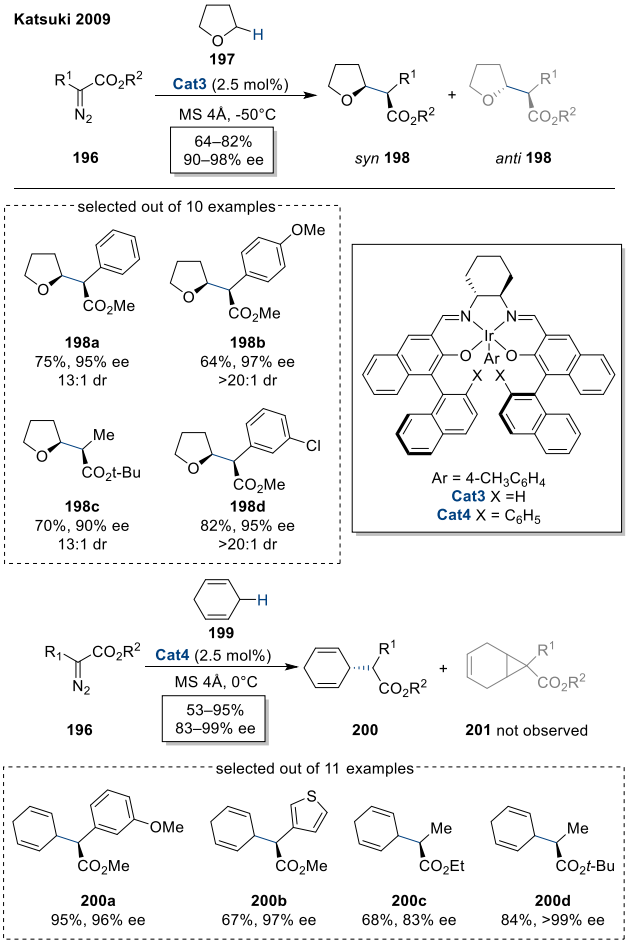
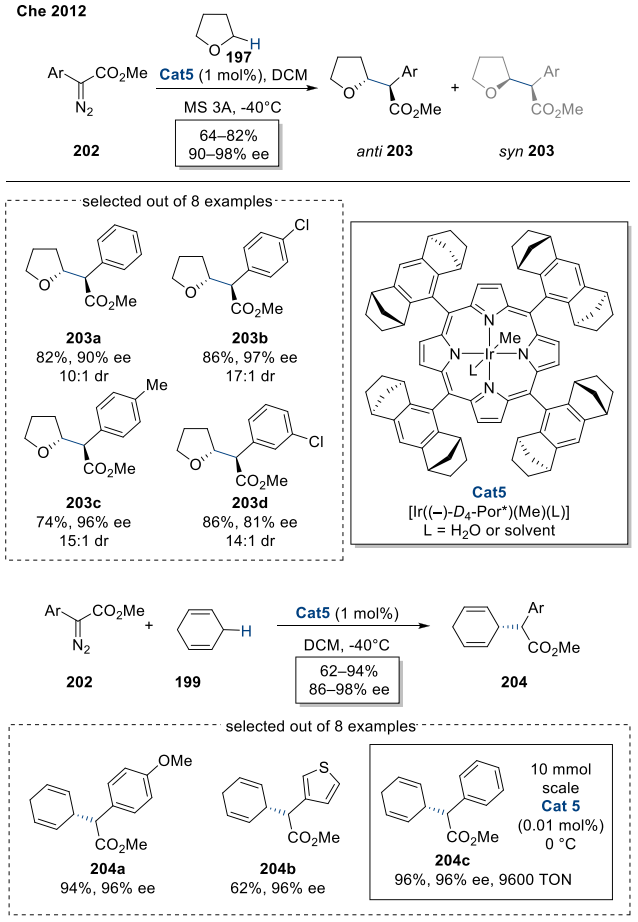
Scheme 37. Ir-Salen Catalyzed C−H Insertion into THF and Cyclohexadiene



Scheme 38. Chiral Iridium Porphyrin Complex Catalyzes an Enantioselective C−H Insertion into THF and Cyclohexadiene

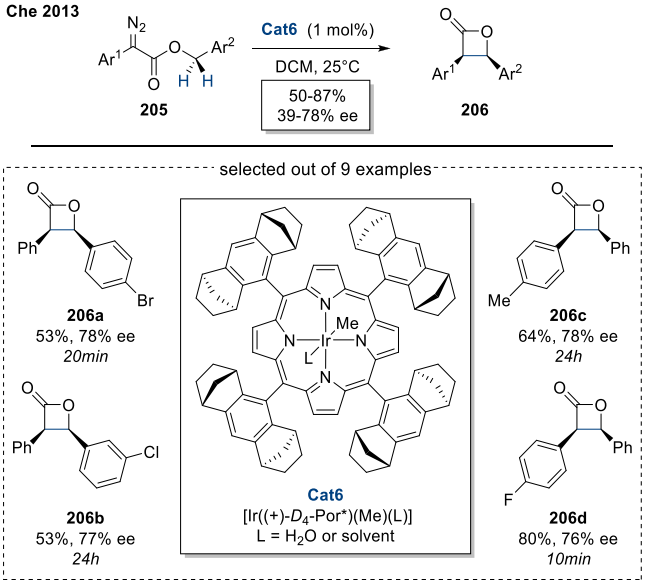


was amenable to a 10 mmol scale (0.01% cat. loading), providing the product **204c** in 96% yield and 96% ee (i.e., TON = 9600). Complementary to Katsuki's Schiff-base complexes, the iridium porphyrin **Cat5** affords the THF-derived products with a predilection for the *anti*-diastereoisomers. Consequently, these strategies enable the synthesis of all stereoisomers of these products by selecting an appropriate ligand environment.

Che and co-workers expanded their catalytic system to an intermolecular C−H insertion process, leading to enantioenriched *cis*-β-lactones (Scheme 39).[134] Substitution on both the benzyl ester and diazo-aryl portions was examined, revealing that the reaction rate and enantioselectivity were strongly affected by the nature of the substituents. Substrates bearing electron-withdrawing groups in the *para*-positions of the aromatic rings convert smoothly into products **206** with good yields (53−86%) and good enantioselectivities (76−78% ee). *Ortho*- and *meta*-substituted substrates, as well as those with an electron-donating group in the *para*-position, require an increased reaction time (up to 24 h) and provide the β-lactones with moderate yields (58−76%) and enantiomeric excesses (39−77% ee).

Blakey, Davies, Musaev, and co-workers developed a library of iridium(III) phebox complexes,[135,136] successfully employed in enantioselective C−H insertions of aryl substituted α-diazoesters into cyclohexadienes (Figure 1).[137] The phebox ligands[138,139] provide an easily tunable platform, regarding steric and electronic modulation, and form air and moisture stable iridium complexes which in turn are compelling catalysts to

Scheme 39. Ir-(+)-(D_4-Por*(Me)) Catalyzed Intramolecular C−H Insertion into α-Diazoesters



widely explore in enantioselective C−H insertion processes. The reaction tolerates various substituents on the aromatic ring and ester moiety, providing products **204** with high yields (10−99%) and good to excellent enantioselectivities (83−99% ee).

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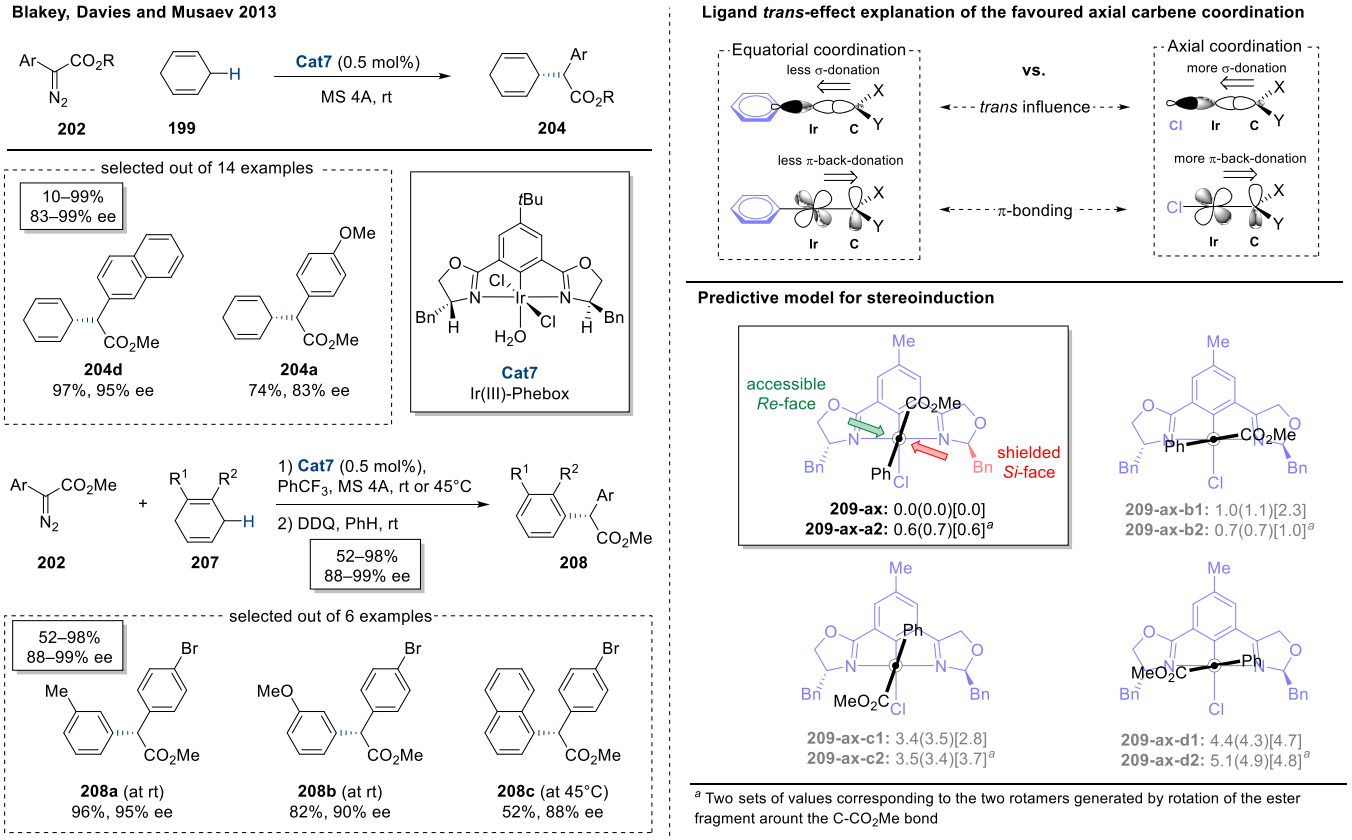
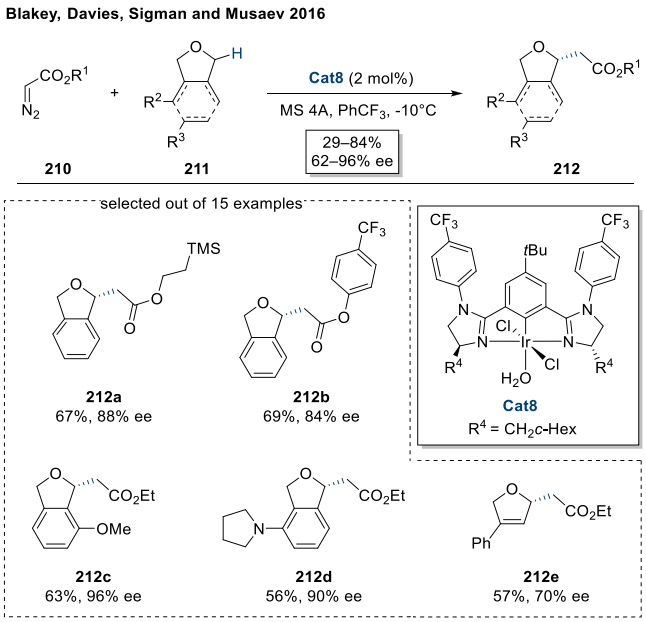


Figure 1. Ir-phebox catalyzed C−H insertion into cyclohexadiene and various polyenes. Electronic influence of ligand results in axial carbene coordination and calculated conformers $\Delta E(\Delta H)[\Delta G]$ (kcal·mol^{-1}) relative to the most stable axial coordinated complex 211ax and suggested approach of the incoming substrate.

Scheme 40. Ir(III)-bis(imidazolinyl)phenyl Catalysts for Enantioselective C−H Functionalizations with Ethyl Diazoacetate



The authors extended the scope to substituted cyclohexadiene substrates **207**, displaying excellent regiocontrol. In these cases, the enantioselective C−H insertion process is followed by a subsequent oxidation to form ester products **208**, bearing two differently substituted aryl groups in the α-position. Computational studies provided a better understanding of the observed stereochemical induction. The authors established that the carbene is likely to adopt an axial position. This is due to a stronger σ-donation to the iridium center, favored by the *trans*-chloride ligand synergistically accentuated by stronger π-back-donation from the metal resulting in a stronger metal−ligand interaction (Figure 1). A conformational analysis of the resulting complex, with the carbene ligand bound in the axial position, gave rise to a predictive model, which explains the high selectivity observed in the formation of the (*R*)-product. The most stable conformation of the axial iridium carbenoid **209ax** indicated that the benzyl substituent of the ligand shields the *Si*-face of the reactive center, exposing the *Re*-face to reaction with the cyclohexadiene (Figure 1).

A similar strategy was further developed for the asymmetric C−H functionalization with acceptor-only metallocarbenes,[140] which had never been employed in enantioselective C−H insertion processes.[141,142] The challenges associated with acceptor-only diazo compounds are the high electrophilicity, as well as the reactivity of the resulting carbenoid centers, which result in inherent chemoselectivity issues. Moreover, these substrates are not prochiral, hence the enantioselectivity of the processes depends on the ability of the chiral catalyst to differentiate among orientations of the incoming substrate. Through means of iridium catalysis, these challenges have been addressed. The third-row metal carbenoids tend to possess lower electrophilicity, due to the increased metal to ligand back bonding, which also increases the barriers for the subsequent group transfer process, facilitating the selectivity control.

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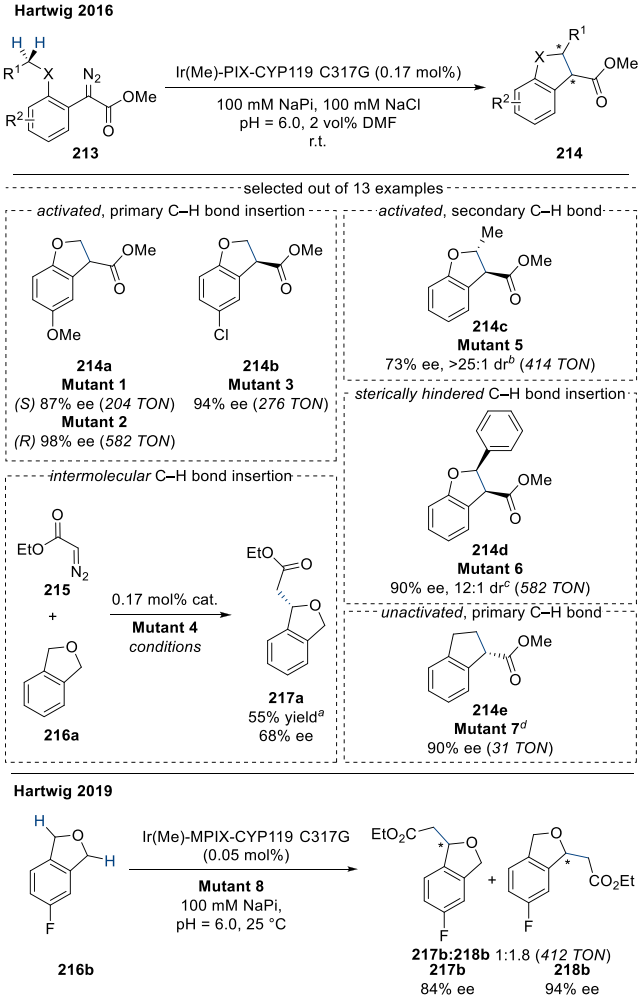
Scheme 41. Enzymatic C−H Insertion Catalyzed by an Engineered Ir-CYP450 Complex

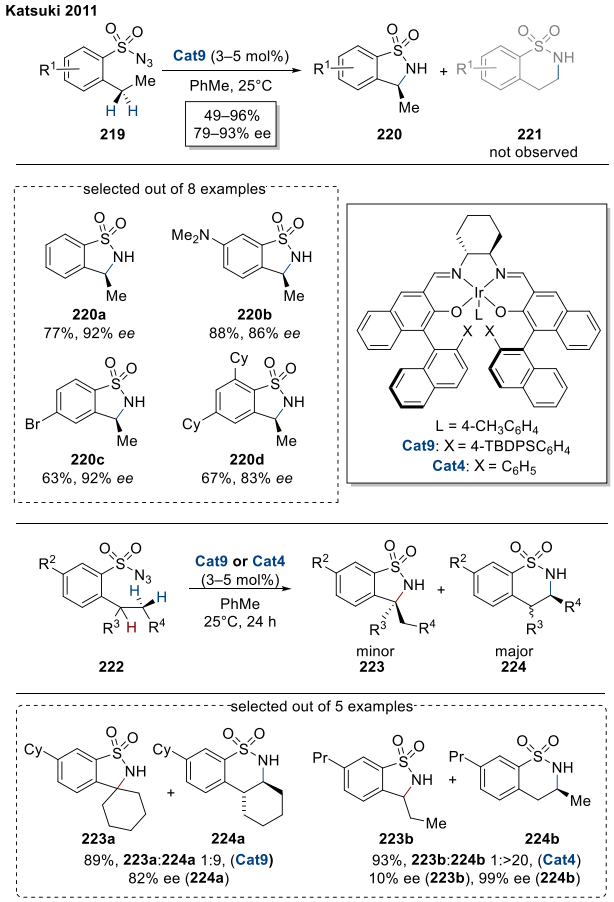


Mutant 1: 213A, 254L; **Mutant 2**: 69Y, 213G, 152W; **Mutant 3**: 69Y, 213G, 152W; **Mutant 4**: 69V, 213A, 254L, A152W; **Mutant 5**: 69W, 213G, 318G; **Mutant 6**: 69W, 213G; **Mutant 7**: 69V, 213G, 254L; **Mutant 8:** C317G, T213G, V254A, A152L, 252S. [a] 120:1 product:carbene dimer; [b] dr = trans:cis; [c] dr = cis:trans; [d] 1 mol% cat., 37° C, 16h;

Mutant 1: 213A, 254L; Mutant 2: 69Y, 213G, 152W; Mutant 3: 69Y, 213G, 152W; Mutant 4: 69V, 213A, 254L, A152W; Mutant 5: 69W, 213G, 318G; Mutant 6: 69W, 213G; Mutant 7: 69V, 213G, 254L; Mutant 8: C317G, T213G, V254A, A152L, 252S. [a]120:1 product:carbene dimer; [b]dr = trans:cis; [c]dr = cis:trans; [d]1 mol% cat., 37° C, 16 h.

Supported by computational studies, the authors designed the Phebim (bis(imidazolinyl)phenyl) complex **Cat8**, enabling a highly enantioselective C−H insertion of acceptor-only diazoacetates **210** into phthalan and dihydrofuran derivatives **212** (Scheme 40). Specifically, calculations indicated that the favored transition state involves electrostatic interaction between the oxygen atom of the THF with one of the hydrogen atoms located at the stereogenic centers of the ligand. The authors postulated that modulation of the electronic properties of the imidazoline moiety can influence this interaction, which led to the development of the successful ligand bearing 4-trifluoromethyl phenyl substituent. Moreover, the authors utilized linear regression mathematical modeling techniques, which suggested that the unusual CH_2*c*-Hex substituent on the imidazoline ring of the catalyst is optimal for the reaction.

Scheme 42. Ir-Salen Complex Catalyzed Regio- and Enantioselective Intramolecular Sulphonamidation of C(sp^3)−H Bonds



Enantioselective iridium carbenoid C−H insertions have been drawing attention as valuable methodologies for the activation of C−H bonds and have been under investigation with the aim to expand them to a wider range of substrates. In this regard, enzymatic catalysis provides interesting opportunities. In 2016, Hartwig and co-workers presented a library of engineered variants of P450 enzymes CYP119 containing iridium as a metal, in place of iron (Scheme 41).[143] These enzymes play a key role in metabolism[144] and are also well-known to oxidize C−H bonds in complex natural products.[145] After conducting a directed evolution methodology, several mutants, allowing for the formation of both enantiomers of the products with excellent enantiomeric excesses, were identified. Notably, the affinity of these new enzymes for the abiological substrate **213** was even higher than that of the natural iron containing P450-BM3 enzyme for its own substrate (lauric acid). The intramolecular carbenoid insertion into the ethereal C−H bond in dihydrobenzofuran proceeds with high turnover numbers (up to 600 TON) and high to excellent enantioselectivities (87−98% ee), indicating only a small influence of the aryl ring substituents on the process. Insertion into the secondary C−H bond gives the product **214c** in high diastereo- and enantioselectivity (>25:1 dr, 73% ee, 414 TON). A sterically hindered C−H bond is also amenable to insertion, providing the *cis* product **214d** in high diastereo- and enantioselectivity (12:1 dr, 90% ee, 582 TON). Insertion also proceeds into an unactivated C−H bond, which signifies the first report of a metal catalyst affording an indane **214e** via carbene insertion with

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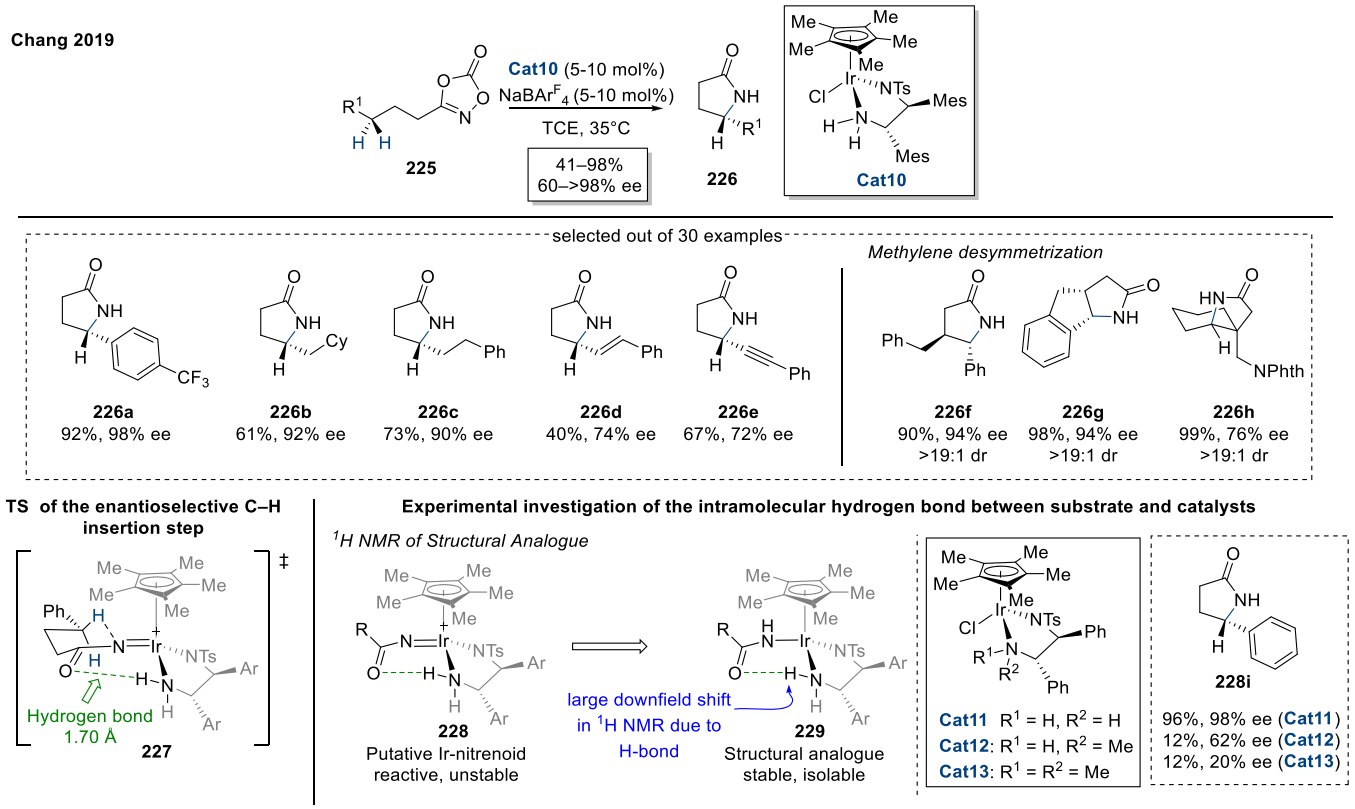
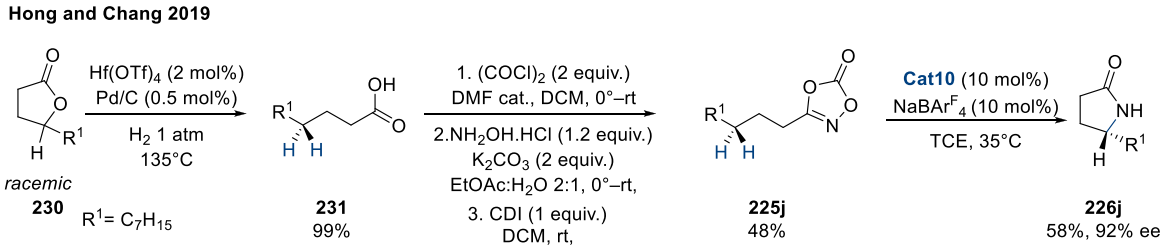
Scheme 43. Enantioselective C−H Amidation of Dioxazolones to Form γ-Lactams



Scheme 44. Application of Iridium Catalysis in Enantioselective Lactone-to-Lactam Conversion



meaningful enantioselectivity (90% ee, 31 TON), without requiring the installation of a chiral auxiliary. An intermolecular C−H insertion of ethyldiazoacetate **215** into phtalan **216a** proceeds with moderate yield (55%) and enantioselectivity (68% ee) without forming the carbene dimer.

Performing the model reaction on scales varying from 0.5 mg to 1 g affects neither the high enantioselectivity nor the moderate yield (48−60% yield, 92−94% ee,). Low catalyst concentration (0.0025 mM) with a substrate concentration of 100 mM still affords the insertion product in good yields and high enantioselectivity (76% yield, 92% ee, 30293 TON). The carbene insertion is thus amenable to a practical preparative scale. Eventually, the supported catalyst on CNBr-activated sepharose gives the product in moderate yield and good enantioselectivity (52%, 83% ee), enhancing the potential for catalyst recyclability. In 2019, the same group reported a similar strategy for the site selective functionalization of C−H bonds with nearly identical steric and electronic environments (Scheme 41).[146] The reported example using 4-fluorophthalan **216b** yields two constitutional isomers **217b** and **218b** with low chemoselectivity (1:1.8), but with high enantiomeric excess (84% ee and 94% ee).

3.2. Reactions of Iridium Nitrenoids

The insertion of metal nitrenoids into C−H bonds is a powerful strategy to construct chiral amines. Organic azides have long been used as efficient and inherently "green" precursors for nitrenes,[147] which have found extensive applications in enantioselective C−H amination chemistry.[148] In 2011, Katsuki reported the first regio- and enantioselective C−H amination of azides by means of iridium catalysis. Cyclization of 2-ethylbenzenesulfonyl derivatives **219**, in the presence of the iridium-salen complex **Cat9**, exclusively gives five-membered benzosultams **220**, via the insertion of the iridium nitrene into the benzylic C−H bonds, with good yields and high enantioselectivities (49−96% yield, 79−93% ee) (Scheme 42).[149] The reaction tolerates a range of substituents at different positions in the aromatic ring. However, upon extending the 2-alkyl group from ethyl to cyclohexyl or *n*-propyl, the nitrene insertion takes place predominantly at the homobenzylic position, giving rise to the six-membered sultam products **224**. For some substrates, e.g. **222b**, switching from **Cat9** as catalyst to the less bulky **Cat4** improves the regioselectivity of the process, while maintaining the high enantioselectivity of the

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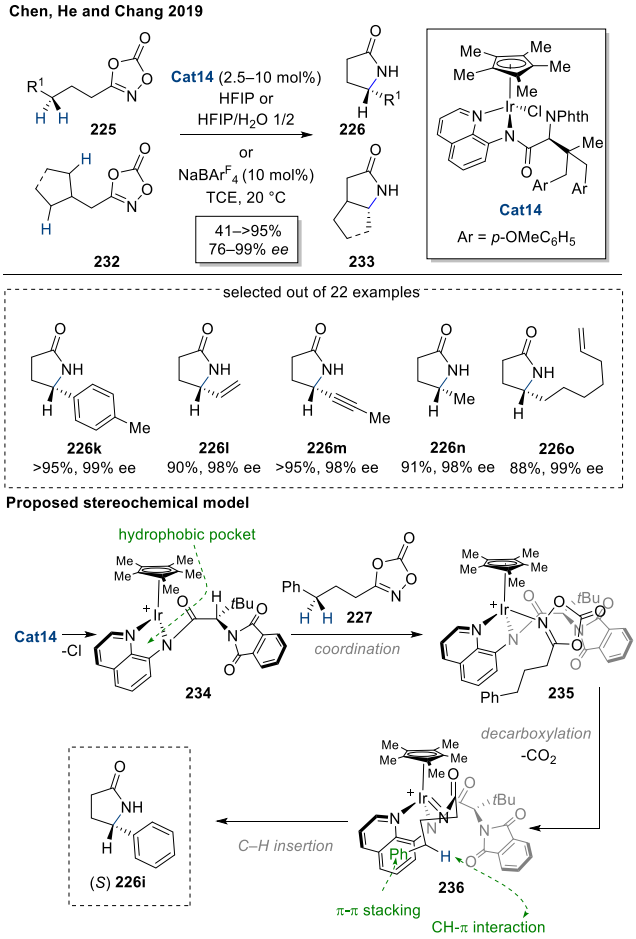
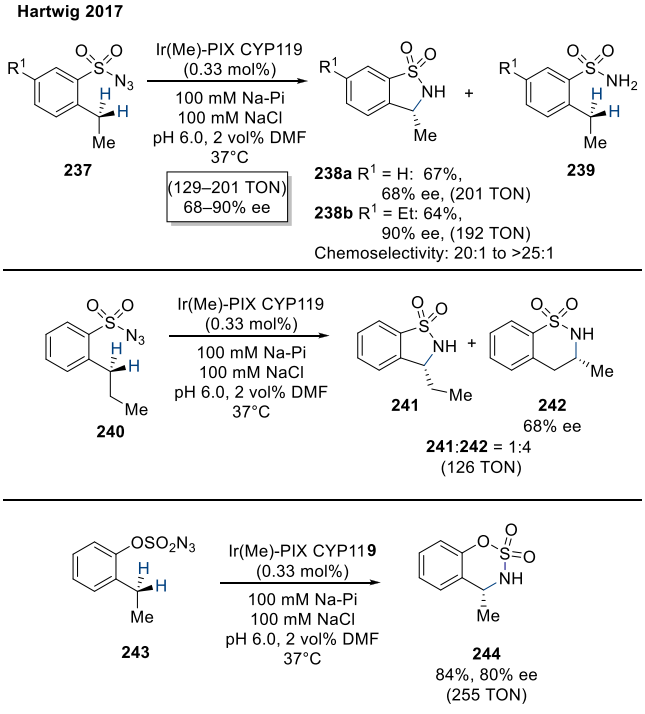
Scheme 45. A New α-Amino-Acid-Cased Ligand Enables a Highly Enantioselective Ir-Catalyzed C−H Amidation of Dioxazolones



Scheme 46. Enzymatic Amination of C−H Bonds



major product **224b**. This indicates that the stereoselectivity of this process strongly depends on the ability of the chiral iridium carbenoid to adopt a suitable conformation for the efficient orbital interaction with the particular C−H bond. This appropriate conformation may vary with the structure of the substrate and the catalyst.

Aside from the preparation of chiral sultams, the development of catalytic enantioselective methodologies for the generation of enantioenriched γ-lactams has also been sought after. γ-Lactam is an effective motif found in various anticancer drugs.[150] Recent developments of enantioselective C−H amidations have offered valuable alternatives to the existing strategies for the synthesis of this structural motif.[73,151−153] In 2019, Chang reported the use of the Ir complex **Cat10**, bearing a chiral diamine ligand, to access chiral γ-lactams from dioxazolone substrates **225** in a highly enantioselective manner (Scheme 43).[154] Dioxazolones are safer and more thermally stable precursors of acyl nitrenes than acyl azides.[155] The reaction proceeds smoothly under air to give cyclic lactams **226** with high yields and enatioselectivities (41−98% yield, 60−>98% ee). The chiral iridium nitrenoid reacts with various enantiotopic aliphatic and benzylic C−H bonds with high selectivities, however, the functionalization of the allylic and propargylic positions yields products **226d** and **226e** with lower enantiomeric excesses (72−74% ee). Substrates bearing enantiotopic methylene groups undergo desymmetrization to give the lactam products with two consecutive stereocenters. Computational studies indicated an importance of a hydrogen bond interaction between the substrate's carbonyl group and the chiral diamine ligand, which stabilizes the transition state leading to the major (*S*) enantiomer of the product (Scheme 43). This was further supported by direct observation of the key hydrogen bond interaction in complex **229**, which is structurally analogous to the reactive intermediate **227**. Moreover, iridium catalysts **Cat12** and **Cat13**, bearing *N*-alkylated ligands, yield the product with substantial erosion of enantioselectivity (Scheme 43).

Soon after, Chang, Hong, and co-workers applied this methodology to convert γ-lactones to γ-lactams.[156] The reaction sequence starts with the reductive opening of the lactones in the presence of catalytic Pd/C and $Hf(OTf)_4$ under a hydrogen atmosphere. The resulting carboxylic acids **231** are then converted into dioxazolones **225j** in three steps. The following C−H amidation leads to the γ-lactams. Application of the chiral iridium catalyst **Cat10** gives the enantioenriched product **226j** in 58% yield and 92% ee (single example, Scheme 44).

In the same year, Chen, He, Chang, and co-workers disclosed the intramolecular C−H amidation of dioxazolones, employing a new chiral iridium catalyst **Cat14**, composed of an α-amino-acid-based ligand (Scheme 45).[157] The *N*,*N*-bidentate aminoquinoline (AQ) ligand, coupled with a phthalazine-protected L-*tert*-leucine derivative, forms a well-defined groove-type chiral pocket around the iridium center. The dioxolone substrates, dissolved in a polar reaction medium (hexafluoroisopropanol-HFIP, or mixed HFIP/H_2O), readily enters the chiral, hydrophobic pocket of the catalyst **234** to form a substrate/catalyst complex **235**. The subsequent decarboxylation leads to the reactive iridium carbenoid species **236**. Computational analysis revealed multiple noncovalent interactions between the chiral ligand and the substrate in the transition state, leading to the product. The phenyl group of the substrate **225** was found to engage in a π-stacking interaction with the AQ plane and Cγ(sp^3)−H bond of **236**, to build an attractive H/π interaction with the phthalimide group (Scheme 45). This catalytic system

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allows for the conversion of a broad range of dioxazolones into enantioenriched γ-lactams with high yields (41−95%) and enantiomeric excesses (76−99%), including the previously problematic substrates containing allylic, propargylic, and nonactivated aliphatic C−H bonds (Scheme 43).

A different strategy for the enantioselective sulfonamidation of C−H bonds was demonstrated by means of enzymatic catalysis. In 2017, Hartwig disclosed an engineered iridium porphyrin cofactor (Ir(Me)-PIX), contained within the protein CYP119 mutants, which catalyzes an enantioselective C−H sulfonamidation of sulfonyl azides (Scheme 46).[158] The C−H insertion proceeds preferentially over the undesired reduction of the sulfonyl azides to sulfonamides **239**, which is a competing pathway typically found in C−H nitrene insertions catalyzed by Fe metalloenzymes.[159] Sulfonyl azides, bearing alkyl substituents on the aromatic ring, can be transformed into five-membered ring sultams with good enantioselectivities (68−90%) and catalyst turnovers (129−201 TON). The application of 2-propylbenzenesulfonyl azide **240**, however, leads to six-membered sultam as the major product, in moderate enantioselectivity (68% ee). In addition, sulfamate azide **243** gives rise to benzyl sulfamate **244**, which can be readily transformed into various benzyl amines.[160] Notably, this enzymatic process relies on the iridium porphyrin cofactor, although the iridium-nitrene C−H insertions by porphyrin complexes are not known.

4. CONCLUSIONS AND FUTURE OUTLOOK

The catalytic enantioselective functionalization of C−H bonds by chiral iridium complexes has become a valuable strategy for the construction of chiral molecules. Following the pioneering studies from the beginning of this century, the field has been evolving dynamically over the last ten years. Employing various chiral ligand classes, including commercially available structures such as BINAP, SEGPHOS, or QuinoxP, as well as newly developed chiral dinitrogen-, phosphine, boryl-, or Cp^x-ligands, has enabled a wide range of C−H functionalization processes with high enantioselectivities. Mechanistic insights into some of these reactions have provided a better understanding of their fundamental steps, as well as explanations of the observed stereoselectivities. This may facilitate the future design of new transformations and chiral ligands, in order to address the remaining challenges in this field. Currently, most of the reported inner-sphere processes require the assistance of a directing group, which is not always a desired part of a target molecule and often must be installed before and removed after the key transformation. The development of nondirected enantioselective C−H functionalization reactions would enable broader applications of this technology. Moreover, the introduction of a transient directing group strategy[161−163] to enantioselective iridium-catalyzed C−H functionalizations could open new synthetic opportunities. Enzymatic catalysis, as well as an emerging approach, which relies on noncovalent interactions between the substrate and chiral ionic catalyst, indicates interesting directions for possible innovations. A quantitatively driven catalyst design would greatly contribute to the development of new processes by shortening the time for the ligand and reaction optimizations in comparison to an intuition-guided approach.[164] Additionally, a deeper understanding of the reactivity differences between the group 9 elements would contribute to the rational design of new enantioselective processes. We expect that future developments of the enantioselective iridium catalyzed C−H functionalizations will provide useful solutions to the stereoselective synthesis of relevant chiral molecular scaffolds.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

Biographies

Łukasz Woźniak was born in Kościerzyna, Poland. He received his B.Sc. from the University of Gdańsk and his M.Sc. from Jagiellonian University. He earned his Ph.D. in 2017 under the supervision of Prof. Paolo Melchiorre at the ICIQ, Tarragona (Spain), working on enantioselective catalysis of photochemical reactions. In 2018, he joined the laboratory of Prof. Nicolai Cramer as a postdoctoral researcher where he focuses on the development of enantioselective C−H functionalization methodologies.

Jin-Fay Tan obtained his B.Sc. in pharmacy with honors (first class) from National University of Singapore. Under the tutelage of Prof. Brian Dymock, his bachelor thesis focused on the design and total synthesis of dual hybrid inhibitors as potential anticancer agents. He then carried out a one-year internship at Institute of Chemical and Engineering Sciences, Singapore. In late 2017, he began his Ph.D.

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studies in the group of Prof. Nicolai Cramer, exploring applications of 1-alkynyl triazenes in transition metal-catalyzed transformations.

Qui-Hien Nguyen spent his undergraduate years and obtained his MChem (first class) from the University of Southampton (UK) in 2016. His master project was carried out under the guidance Prof. Bruno Linclau, on the synthesis of UDP-difluorinated galactoses. He spent an intern year at Merck Chemicals Ltd. in Chilworth, UK. He is now studying for his Ph.D. in the group of Prof. Nicolai Cramer, researching asymmetric palladium catalysis.

Adrien Madron du Vigné received both his B.Sc. in chemistry and his M.Sc. in biomolecules chemistry from the National Graduate School of Montpellier (ENSCM) in France. His bachelor thesis was oriented toward the multistep synthesis of biologically interesting carbohydrate mimics used in chaperone therapy to prevent protein misfolding, under the supervision of Prof. Philippe Compain at the University of Strasbourg. He subsequently carried out several industrial placements in Sanofi-Aventis (Frankfurt), Janssen Pharmaceutica (Beerse), and later SpiroChem AG (Basel) for his master thesis. He started his Ph.D. in Prof. Nicolai Cramer's group in late 2019, currently investigating the development and applications of new chiral carbene ligands for asymmetric catalysis

Vitalii Smal received his B.Sc. from Kyiv Polytechnic Institute in 2016, and his M.S. degree in 2018 from École Polytechnique. During his bachelor studies, he worked on organophosphorus chemistry with Dr. Nataliya Shtil. After graduation, he went to France for his masters and studied asymmetric gold(I) catalysis with Dr. Xavier Guinchard. He joined the Cramer group in February 2018 firstly for his master thesis and subsequently continued his Ph.D., researching the applications of new chiral phosphine ligands for asymmetric catalysis.

Yi-Xuan Cao received his B.Sc. from University of Science and Technology of China in 2017, and his M.S. degree in 2019 from University of Rennes 1. During his bachelor studies, he focused on transition metal catalyzed organic fluorine chemistry with Prof. Xi-Sheng Wang. After graduation, he went to Rennes, France, for his masters and studied photoredox catalysis on the modification of acridinium salts with Dr. Jean-François Soulé and Prof. Pierre Dixneuf. He joined the Cramer group in October of 2019 and is now researching the applications of new chiral carbene ligands for asymmetric catalysis.

Nicolai Cramer studied chemistry at the University of Stuttgart, Germany, and earned his Ph.D. in 2005 under the guidance of Prof. Sabine Laschat. He then completed a postdoctoral stint with Prof. Barry M. Trost at Stanford University. From 2007 to 2010, he worked on his habilitation at ETH Zurich, Switzerland, associated with the chair of Prof. Erick M. Carreira, receiving the *venia legendi* in 2010. Subsequently he moved to EPFL (Lausanne, Switzerland) as assistant professor. He was promoted to associate professor in 2013 and to full professor in 2015. Nicolai Cramer's research encompasses the development of sustainable enantioselective metal-catalyzed transformations and their implementation in the synthesis of biologically active molecules. A focus of his research is dedicated to asymmetric C–H functionalizations with abundant metals enabled by novel ligand designs.

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ABBREVIATIONS

AQ	8-aminoquinoline
Ar^F	3,5-bis(trifluoromethyl)phenyl
BTFM	bis[3,5-bis(trifluoromethyl)phenyl
Boc	*tert*-butyloxycarbonyl
CDI	1,1′-carbonyldiimidazole
CMD	concerted metalation-deprotonation
coe	cyclooctene
cod	1,5-cyclooctadiene
Cp	cyclopentadienyl
Cp*	pentamethyl cyclopentadienyl
Cp^x	chiral cyclopentadienyl
CPME	cyclopentyl methyl ether
DABCO	1,4-diazabicyclo[2.2.2]octane
DCE	1,2-dichloroethane
DCM	dichloromethane
DFT	density functional theory
DG	directing group
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DTBM	3,5-di-*tert*-butyl-4-methoxyphenyl
ee	enantiomeric excess
Fc	ferrocene
HAT	hydrogen atom transfer
HFIP	hexafluoroisopropanol
KIE	kinetic isotope effect
Mes	mesityl
MS	molecular sieves
MTBE	*tert*-butyl methyl ether
Pin	pinacol,2,3-dimethyl-2,3-butanediol
Phth	phthalazinyl
r.t.	room temperature
TBDPS	*tert*-butyldiphenylsilane
TCE	1,1,2,2-tetrachloroethane
THF	tetrahydrofuran
Tf	trifluoromethylsulfonyl
Tol	*p*-tolyl,4-methylphenyl
TON	turnover number
Ts	tosyl,*p*-toluenesulfonyl
TS	transition state
Xyl	3,5-xylyl

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